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No.
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In the Supreme Court of the United States

APOTEX, INC. and APOTEX CORP.,

Petitioners,

v.

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Respondents.

On Petition for a Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Under the Patent Act, "a patent may not be obtained" if its subject matter is "obvious" when judged in light of the prior art. 35 U.S.C. § 103. In *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007), this Court addressed several "fundamental misunderstandings" in the Federal Circuit's long-standing approach to this nonobviousness requirement, including its mistaken view that "a patent claim cannot be proved obvious merely by showing that the combination of elements was 'obvious to try.'" *Id.* at 421-422. In this case, the Federal Circuit, without even acknowledging that admonition, held that a chemical substance, once isolated, was nonobvious without any regard to "whether . . . it may have been 'obvious to try'" isolating the substance. App., *infra*, 27a. Its rationale was that certain properties of the isolated substance were not predictable. The question presented is:

> Whether, if an experiment was "obvious to try," a *prima facie* case of obviousness is automatically rebutted by a showing that the outcome of the experiment was not entirely predictable.

RULE 29.6 STATEMENT

The ultimate parent of petitioners Apotex, Inc. and Apotex Corp. is Sherfam Inc., which is not publicly traded. No publicly traded company owns 10% of the shares of petitioners or of any of their parent corporations.

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OPINIONS BELOW

The opinion of the Federal Circuit (App., *infra*, 1a-30a) is reported at 550 F.3d 1075. The district court's opinion (App., *infra*, 31a-124a) is reported at 492 F. Supp. 2d 353.

JURISDICTION

The judgment of the court of appeals was entered on December 12, 2008. App., *infra*, 1a. On March 26, 2009, the court of appeals denied a timely petition for panel rehearing and rehearing en banc. App., *infra*, 125a-126a. On May 29, 2009, the Chief Justice extended the time to petition for a writ of certiorari to and including July 24, 2009. This Court's jurisdiction is invoked under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS INVOLVED

Section 103 of Title 35 of the United States Code provides, in pertinent part:

> (a) A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT

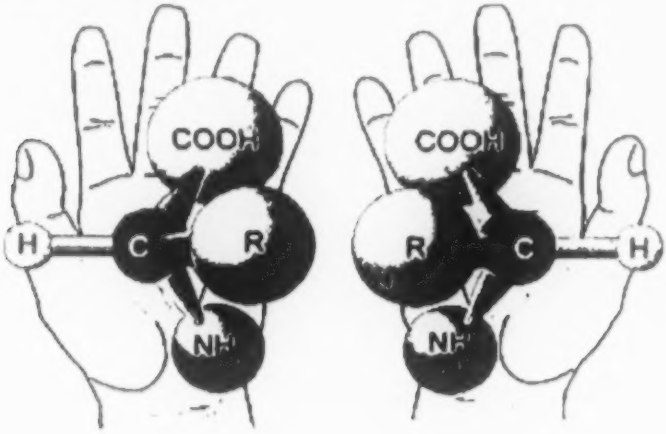
The question presented in this case arises

constantly in patent litigation. If an experiment is prompted by common knowledge in a field but its results cannot be predicted until the experiment is performed, does patentability turn on the *outcome* of the experiment, or is the inquiry rather whether the experiment was "obvious to try" in the first place? *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (2007), supplies a clear answer to this question, and yet the Federal Circuit addresses it in different ways depending on the particular three-judge panel that happens to hear a case. That confusion is entrenched; the Federal Circuit has repeatedly declined to review this issue en banc.

In this case, respondents (collectively "Sanofi") already had a patent on a substance that had shown promise as an anti-blood-clotting agent (*i.e.*, a blood thinner) and that was known to be a mixture of two closely related molecules. After obtaining that patent – which covered not just the mixture but each of the two constituent molecules – Sanofi isolated the two constituents, and found that one had especially pronounced anti-blood-clotting effects, whereas the other was inactive or toxic. Sanofi then obtained an additional patent that covered only the beneficial molecule in isolation. That molecule became the basis of the blockbuster blood-thinning drug Plavix. Plavix, however, was also protected by the first patent, which by itself gave Sanofi many highly profitable years of market exclusivity. The second patent's only function has been to prolong Sanofi's monopoly by eight years, and the question is whether the Federal Circuit correctly analyzed the validity of that patent.

A. Background Principles

Many organic molecules, including many drugs, exist in two forms that are exact mirror images. The two are alike in every way except for their spatial orientation: as with the left and right hand, the forms cannot be superimposed on each other. (This type of spatial asymmetry is known as "chirality." Many everyday objects, such as screws and airplane propellers, are chiral.) The two forms of such a molecule are called enantiomers, and can be described (depending on the direction in which they rotate polarized light) as either "left-handed" (or "levorotatory") or "right-handed" (or "dextro-rotatory"). *E.g.*, WILLIAM H. BROWN, ORGANIC CHEMISTRY 266-268, 278-279 (1995); App., *infra*, 8a. Here, for example, is a schematic illustration of the "handedness" of the enantiomers of a simple amino acid structure:



A substance consisting of an equal mixture of two enantiomers is called a "racemic" mixture, or a "racemate." *E.g.*, App., *infra*, 8a. The parties dispute whether, given a patent on a racemic mixture and its

constituent enantiomers, a later patent on only one of the enantiomers in isolation was obvious.

Enantiomers of the same molecule can have dramatically different biological effects. A notorious example is thalidomide, a tranquilizer that was marketed around the world from 1957 to 1961. *E.g.*, William A. Silverman, *The Schizophrenic Career of a "Monster Drug,"* 110 PEDIATRICS 404, 405-406 (2002). Thalidomide is a racemate, but it is believed that only the left-handed enantiomer is responsible for the sedative effects, whereas the right-handed twin produces birth defects. *E.g.*, John M. Brown & Stephen G. Davies, *Chemical Asymmetric Synthesis*, 342 NATURE 631, 631 (1989). Such "stereoselectivity" is common (if not usually so disastrous) in the world of organic chemistry and has been recognized by chemists for decades. See App., *infra*, 56a. "For racemic drugs, most often only one enantiomer exerts the beneficial effect, whereas the other enantiomer either has no effect, or exerts a detrimental effect. Thus, enantiomerically pure drugs should, more often than not, be more effective than their racemic counterparts." BROWN, *supra*, at 300.

For this reason, in February 1987 the U.S. Food and Drug Administration, following discussions with industry representatives, advised that sponsors of a new drug substance should "have either separated the various potential" enantiomers of the substance "or synthesized them independently." C.A. App. 17548. The agency also noted that individual enantiomers "may need to be studied for pharmacological and toxicological properties (and/or for safety and efficacy)." *Ibid.* Given these scientific and regulatory realities, "many drug companies have decided to

develop only single enantiomers of new chiral drugs." BROWN, *supra*, at 300.

B. The Patents Covering Plavix

Sanofi was no exception. On July 16, 1985, Sanofi was granted a patent on a substance known as PCR4099 and its chemical relatives, which were found to inhibit the aggregation of blood platelets. App., *infra*, 47a; Supp. App. S1, S3 col. 3 ll. 36-57; Supp. App. S12. The patent (U.S. Patent No. 4,529,596, or "the '596 patent") and its foreign counterparts (together, the "Aubert patents") acknowledged that PCR4099 and its relatives are chiral molecules that may exist in the form of two enantiomers, and claimed not only "both enantiomeric forms" of these compounds but also "their mixture." *E.g.*, Supp. App. S2 col. 1 ll. 38-41, S8 col. 13 ll. 17-18. The Aubert patents also claimed PCR4099's (and its enantiomers') "salts [formed from] pharmaceutically acceptable . . . acids." *Id.* at S8 col. 13 ll. 8-10; see also Supp. App. S23.[1]

Although the Aubert patents potentially covered a large number of chemical substances, it was clear that PCR4099 in particular merited further attention. The patents used it as their lead example of the class of molecules, and reported the results of

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[1] Drugs are commonly administered in the form of a "salt," which in chemical parlance refers to the product of a reaction between an acid and a base. Where, as here, the drug in question is a base, a pharmaceutical salt is formed by reacting it with an acid. See, e.g., Note, *"Obvious to Try": A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2625, 2649 n.164 (2008) (citing WERMUTH & STAHL, INTRODUCTION TO HANDBOOK OF PHARMACEUTICAL SALTS: PROPERTIES, SELECTION, AND USE 1 (2002)).

tests in which PCR4099 exhibited very favorable anti-clotting activity. *E.g.*, Supp. App. S6-S7. In July of 1985, Sanofi promoted PCR4099 (but no other compound covered by the Aubert patents) in a paper and at a conference. App., *infra*, 54a. It was common knowledge, however, that drugs that appeared safe could exhibit serious side effects once on the market. *Id.* at 55a. And, as explained above, workers in the industry had strong reasons to try to separate chiral drugs into their enantiomers.

Accordingly, only a few months after obtaining the '596 patent, Sanofi's researchers in November 1985 asked a staff chemist to separate PCR4099 into its constituent enantiomers (which, as noted above, were covered by the Aubert patents). App., *infra*, 9a. He used a technique, known as "diastereomeric salt formation," that originated with Louis Pasteur in the 19th century. *Id.* at 10a. Testing revealed that the dextrorotatory ("right-handed") enantiomer was a highly effective anti-clotting agent whereas the levorotatory ("left-handed") twin had no such effects. At the same time, the left-handed enantiomer was far more toxic than the right-handed twin. *Ibid.* The right-handed enantiomer became known as "clopidogrel," and Sanofi applied for a separate U.S. patent on isolated clopidogrel plus its pharmaceutically acceptable salts. The patent issued on July 11, 1989, as No. 4,847,265 ("the '265 patent"). Supp. App. S29. Sanofi also determined that clopidogrel could be packaged and administered in the form of a bisulfate salt, known as clopidogrel bisulfate.[2] App.,

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[2] As explained in note 1 above, a salt is formed by reacting the drug with an acid. There is nothing particularly remarkable about this process, which is a "common practice in the

infra, 11a. Claim 3 of the '265 patent specifically recites this compound.

In 1997, the FDA approved the sale of clopidogrel bisulfate, which Sanofi exclusively markets as Plavix. App., *infra*, 32a. Plavix is routinely prescribed to treat or prevent heart attacks, strokes, and other cardiovascular events. The '596 patent expired in 2003, *id.* at 34a, but the '265 patent term lasts until 2011, *id.* at 33a.[3]

C. The District Court Proceedings

Petitioners (collectively "Apotex") manufacture and distribute generic drugs. In November 2001, Apotex applied under the Hatch-Waxman Act[4] for FDA approval to market clopidogrel bisulfate following the expiration of the '596 patent (whose validity is undisputed). Sanofi then sued for infringement of the '265 patent, see 35 U.S.C.

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pharmaceutical industry." Note, *"Obvious to Try"*, *supra* note 1, at 2649 n.164; see also *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348, 1353 (Fed. Cir. 2007) ("Active drug molecules . . . are frequently made into pharmaceutically-acceptable acid addition salts to improve their bioavailability."). The FDA has approved a finite set of acids for this purpose. See, *e.g.*, App., *infra*, 73a. The bisulfate (also known as hydrogen sulfate) salt is obtained by reacting the drug with sulfuric acid, which is on the list of FDA-approved acids and was one of the first acids that Sanofi tested. *Id.* at 74a.

[3] That term is 20 years from the date of application (in this case February 12, 1988), see 35 U.S.C. § 154(c)(1), plus an extension to compensate for the FDA review period. See *id.* § 156.

[4] The Act (officially named the Drug Price Competition and Patent Term Restoration Act of 1984) governs the system of generic drugs. Among other things, the Act facilitates challenges to the validity of drug patents. See Pub. L. 98-417, 98 Stat. 1585 (1984).

§ 271(e)(2)(A), and Apotex counterclaimed for a declaration that the patent is invalid. App., *infra*, 3a. The district court held a bench trial, and ruled on June 19, 2007.

Confronting Apotex's obviousness challenge, Judge Stein observed that *Graham* v. *John Deere Co.*, 383 U.S. 1, 17-18 (1966), instructs a court to assess obviousness principally with reference to: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; and (3) the level of ordinary skill in the art. App., *infra*, 102a-103a. Judge Stein then assumed that Apotex had made out a *prima facie* case of obviousness given the prior disclosure of PCR4099 together with "the prior art teachings that (1) racemic compounds may be separated into their enantiomers; and (2) those enantiomers . . . may exhibit different biological activity or different degrees of the same type of biological activity exhibited by the racemate." *Id.* at 106a-107a.

The district court, however, believed that "it is not enough for Apotex to have shown that the [elements] found in Claim 3 of the '265 patent would have been 'obvious to try.'" App., *infra*, 103a. Relying on a series of Federal Circuit cases that antedated *KSR International Co.* v. *Teleflex Inc.*, 550 U.S. 398 (Apr. 30, 2007) – and without even citing *KSR* – the district court reasoned that "evidence of the fact that *any* property of clopidogrel bisulfate is unexpected as compared to PCR4099 or anything else in the prior art rebuts the presumption that clopidogrel bisulfate is obvious in view of its racemate." App., *infra*, 107a (emphasis added). That condition, the court added, was satisfied here because the precise properties of

the two enantiomers as compared with each other and the racemate could not have been "predict[ed] with a reasonable expectation of success." *Ibid.* The '265 patent accordingly was nonobvious, and this was true "[w]hether or not it may have been 'obvious to try' separating the enantiomers of PCR4099 and, secondarily, preparing its dextrorotary enantiomer as a bisulfate salt." *Id.* at 112a. The district court entered judgment in favor of Sanofi. *Id.* at 124a.

D. The Court of Appeals' Decision

The Federal Circuit affirmed. It agreed with the district court that clopidogrel bisulfate was nonobvious regardless of whether the compound was "obvious to try," see App., *infra*, 27a, endorsed the district court's focus on "the unpredictable and unusual properties of the dextrorotatory enantiomer," *id.* at 21a, and rejected Apotex's argument that "the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that enantiomers can exhibit different properties," *id.* at 27a-28a.

The Federal Circuit highlighted testimony to the effect that "the therapeutic and toxic properties of the enantiomers" could not be predicted in advance, that "it was not predictable whether such differences, if any, would be weak, moderate, or strong, or how they would be manifested"; and that so-called "absolute stereoselectivity" (the two enantiomers of the same molecule having completely different biological effects) "is rare." App., *infra*, 23a. On this basis, the Federal Circuit upheld the district court's finding "that a person of ordinary skill in this field would not

reasonably have predicted that the dextrorotatory enantiomer [of PCR4099] would provide all of the [therapeutic] activity and none of the adverse neurotoxicity." *Id.* at 24a.

The Federal Circuit also reached beyond the reasons that the district court gave for holding the patent nonobvious (see App., *infra*, 104a-112a), pointing to the "difficulty" of the enantiomeric separation, and the time and effort needed to perform it. App., *infra*, 25a-26a. And the Federal Circuit agreed with the district court that "Sanofi's expenditure of tens of millions of dollars for several years of development of the racemate PCR4099, before [deciding to try] separating the enantiomers, also weighed against finding that separation would have been obvious," *id.* at 26a; App., *infra*, 108a.

The Federal Circuit also thought that rendering clopidogrel as the bisulfate salt was not obvious because the scientific literature listed many acids "as candidates for forming salts with basic drug compounds," and the parties' experts agreed that it was "unpredictable" whether any "particular acid-base combination" would yield a pharmaceutically suitable salt. App., *infra*, 27a. Finally, the Federal Circuit agreed with Sanofi that *KSR*'s lessons were inapplicable insofar as this case involved a procedure with an unpredictable result rather than a mechanical combination of familiar elements "having the properties of the known components." *Id.* at 29a-30a.

The Federal Circuit denied Apotex's petition for rehearing en banc. App., *infra*, 126a.

REASONS FOR GRANTING THE PETITION

The question presented arises constantly in many industries and has enormous economic importance. In many fields of science and other useful arts, experimenters using known methods frequently do not know how a particular substance or product will behave before they create it. Yet if, as the Federal Circuit's holding would have it, any new compound with at least some unpredictable properties is nonobvious, then nearly *every* new substance would qualify for a patent, and the patent system would "stifle, rather than promote, the progress of useful arts." *KSR Int'l Co.* v. *Teleflex Inc.*, 550 U.S. 398, 427 (2007).

KSR explained that a finding that an approach is "obvious to try" might well suffice to render the resulting invention obvious. The U.S. Patent and Trademark Office has followed suit. But the Federal Circuit has failed to apply that lesson consistently despite repeated unsuccessful requests for rehearing en banc and dissents by some of the court's members. This entrenched confusion harms brand-name product developers and would-be generic competitors; both types of companies make decisions about which products to develop and market based on standards of patentability.

Certworthiness of a Federal Circuit decision is often "found in the Federal Circuit's treatment of patentability standards, or in its treatment of an exceptionally significant patent, or in its application of Supreme Court precedent." EUGENE GRESSMAN ET AL., SUPREME COURT PRACTICE 287 (9th ed. 2007); see also *KSR*, 550 U.S. at 407 ("Because the Court of Appeals addressed the question of obviousness in a

manner contrary to § 103 and our precedents, we granted certiorari."). This case presents every one of those circumstances, and more. This Court should grant review, resolve the confusion in the Federal Circuit's case law, and clarify that *KSR* applies even when certain aspects of the art are inherently unpredictable.

I. The Court of Appeals Has Failed To Heed This Court's Admonition That "Obvious To Try" *Can* Render an Invention Obvious

A. *KSR* explicitly rejected the analysis used below. In *KSR*, the Federal Circuit had deployed a series of doctrines to avoid concluding that a patent was obvious, even though the invention – titled "Adjustable Pedal Assembly With Electronic Throttle Control" – was just a mechanical combination of two already well-known components. See 550 U.S. at 406, 413-415. The Federal Circuit thought it irrelevant "[t]hat it might have been obvious to try the combination of [an adjustable pedal assembly] and [an electronic] sensor," because, according to the Federal Circuit, "'obvious to try' has long been held not to constitute obviousness." *Id.* at 414 (internal quotation marks omitted).

This Court disagreed:

> [T]he Court of Appeals . . . conclude[d], in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill

> has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421 (citation omitted).

The district court and the Federal Circuit flatly ignored this teaching. (The district court ruling did not even cite *KSR*, which antedated the ruling by two months.) See App., *infra*, 103a (quoting Federal Circuit: "We have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. § 103."); App., *infra*, 27a (agreeing that the '265 patent was nonobvious "[w]hether or not it may have been 'obvious to try' preparing clopidogrel bisulfate"). Apotex, however, was entitled to have the courts below ask the questions posed by this Court in *KSR*: whether there was a "design need" or other "pressure" to solve a problem (namely, the isolation of the enantiomers of a promising racemate and the preparation of a pharmaceutically acceptable salt) and a "finite number of identified, predictable solutions" (namely, the reagents and concentrations that one varies in order to separate enantiomers and prepare a pharmaceutical salt) such that Sanofi's workers had good reason "to pursue the known options within [their] technical grasp." Had the courts below asked those crucial questions mandated by *KSR*, they might have recognized that Sanofi's successful enantiomeric separation and salt formation was "the product not of innovation but of ordinary skill and common sense."

B. Instead, the courts below focused on the *outcome* of Sanofi's experiments, and in particular on whether any aspect of that outcome was unexpected. See App., *infra*, 107a ("[E]vidence of the fact that *any* property of clopidogrel bisulfate is unexpected . . . rebuts the presumption that clopidogrel bisulfate is obvious in view of its racemate." (emphasis added)). Yet both sides agree that it was known that the properties (both therapeutic and toxic) of enantiomers often differ, even if the exact nature and degree of difference could not have been known. And it is undisputed that the properties of a racemate are the sum of the properties of its enantiomers. Thus, given a known racemate, the only unknown will be the precise *allocation* of its properties to the enantiomers.[5] In hanging patentability on this "known unknown," the Federal Circuit essentially said that any element of unpredictability or unexpectedness in an experiment suffices to patent the result.

That fixation on unexpectedness or unpredictability has no support in, and in fact clashes with, this Court's decisions. When "the prior art discloses the method of making an article having the characteristics of the patented product," this Court has noted, the patent is invalid, "[even] though all the advantageous properties of the product had not been fully appreciated." *Gen. Elec. Co.* v. *Jewel Incandescent Lamp Co.*, 326 U.S. 242, 248 (1945). In fact, by the end of the 19th century, "nothing [wa]s better settled in this [C]ourt than that the application of an old process to a new and analogous purpose does not

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[5] The testing required to determine those properties once the enantiomers are isolated is routine (if time-consuming), and nobody has suggested otherwise.

involve invention, *even if the new result had not before been contemplated*." *Ansonia Brass & Copper Co.* v. *Elec. Supply Co.*, 144 U.S. 11, 18 (1892) (emphasis added).

This point was appreciated by at least some of the courts of appeals before the Federal Circuit was created. See *Univ. of Ill. Found.* v. *Winegard Co.*, 402 F.2d 125, 127 (8th Cir.) ("The statutory standard of patentability under § 103 is not 'predictability.' . . . Where logical exploration within known principles of the science achieves an unpredictable result, even though a commercially desirable one, the burden of nonobviousness is not necessarily overcome."), cert. denied, 394 U.S. 917 (1969); *Compton* v. *Metal Prods., Inc.*, 453 F.2d 38, 42 (4th Cir.) ("'The ultimate question is whether a hypothetical person having ordinary skill in the art would have readily found the same solution when addressing himself to the same problem.'"), cert. denied, 406 U.S. 968 (1972). Having been rebuffed in *KSR* for according too little weight to the fact that a new approach was "obvious to try," the Federal Circuit has resurrected long-discarded notions to try to rebut the inference that arises from the obviousness of trying a particular approach.

What is more, the Federal Circuit's approach is fundamentally inconsistent with one of *KSR*'s core animating principles: "Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress." 550 U.S. at 419. The whole reason for the nonobviousness requirement is that the patent system is supposed to reward not (as the decisions below seem to have assumed) every single incremental advance, but rather *only advances that would have been less likely*

without the promise of a patent. The "carefully crafted bargain" embodied in the patent system confers exclusive rights for a period of years only as a means to "the ultimate goal" of "bring[ing] new designs and technologies *into the public domain.*" *Bonito Boats, Inc.* v. *Thunder Craft Boats, Inc.*, 489 U.S. 141, 150-151 (1989) (emphasis added); accord *Pfaff* v. *Wells Elecs., Inc.*, 525 U.S. 55, 63-64 (1998). If an invention was going to enter the public domain anyway, then almost by definition a separate patent on it only "retards progress."

The right-handed enantiomer of PCR4099 turned out to be a better drug than the racemic mixture, but there are excellent reasons to believe that Sanofi would have separated PCR4099 into its components (and then selected an appropriate salt) "in the ordinary course." (Those reasons include PCR4099's known properties as a blood thinner, and the potential benefits of separating a racemic mixture into its constituent enantiomers.) And if no additional inducement was needed for this incremental advance, then additional exclusivity cannot possibly promote the purposes of the patent system.

In fact, it is telling that Sanofi would have been rewarded handsomely for its investments even without the later '265 patent. The earlier '596 patent gave Sanofi 20 years of exclusive rights in the United States to PCR4099 and its component enantiomers. That period expired only after Plavix had been on the market for five or six years as one of the world's top-selling drugs – and could have lasted even longer if Sanofi had relied only on the '596 patent to protect Plavix. See note 3, *supra*. Conferring an additional eight years of exclusivity through the '265 patent, see

page 7 *supra*, is an abuse of the patent system's "carefully crafted bargain" – it has postponed competition in the market for an important drug with no corresponding societal benefit.

In sum, the Federal Circuit was quite wrong to distinguish *KSR* on the ground that it involved a mechanistic combination of known components rather than a chemical refinement with a not-fully-predictable result. The basic lesson of *KSR* is that not every incremental advance should qualify for twenty years of exclusivity. That lesson is not limited to mechanical engineering, nor is it any less applicable simply because some aspects of a technology are inherently unpredictable.

C. The approach adopted below runs counter to that of the PTO and contributes to incoherence in the Federal Circuit's case law. Following *KSR*, the PTO issued new examination guidelines for determining obviousness. The guidelines, which cite and closely track *KSR*, are wholly inconsistent with the analysis employed by the courts below. They direct a patent examiner to reject claims as "Obvious To Try" if he or she finds:

> (1) . . . that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
>
> (2) . . . that there had been a finite number of identified, predictable solutions to the recognized need or problem;
>
> (3) . . . that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

> (4) whatever additional findings based on the *Graham* factual inquiries [(see page 8, *supra*)] may be necessary . . . to explain a conclusion of obviousness.

PTO, *Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of [KSR]*, 72 FED. REG. 57526, 57529, 57532 (2007).

As "Example 1" of this analysis, the guidelines discuss *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348 (Fed. Cir.), cert. denied, 128 S. Ct. 110 (2007). In that case, the patentee had argued that the results of forming a particular pharmaceutical salt "would have been unpredictable, and therefore were nonobvious." 75 FED. REG. at 57532. The panel, however, "*rejected the notion that unpredictability could be equated with nonobviousness* here, because there were only a finite number (53) of pharmaceutically acceptable salts to be tested." *Ibid.* (emphasis added). In other words, a degree of unpredictability does not overcome "obvious to try."[6]

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[6] Similarly, the PTO uses as "Example 2" of "Obvious To Try" another Federal Circuit case in which, according to the PTO, "it would have been obvious to try the known methods . . . , with a reasonable expectation of success. The court was not swayed by arguments of a lack of absolute predictability." *Ibid.* (citing *Alza Corp.* v. *Mylan Labs., Inc.*, 464 F.3d 1286 (2006)). Both *Pfizer* and *Alza* were decided between the *KSR* cert. grant and opinion, at a time when Federal Circuit judges had made no secret of their apprehension of a potential reversal in *KSR*. See 550 U.S. at 421 ("We note the [Federal Circuit] has since elaborated a broader conception of [its obviousness] test than was applied in the instant matter." (citing *Alza*)). The PTO's third and final example of "Obvious to Try" was *Ex Parte Kubin*, a PTO administrative appeal since affirmed by the Federal Circuit. The *Kubin* decisions closely track *KSR*'s discussion of "obvious

As if to provide a neat demonstration of the inconsistency in the Federal Circuit's obviousness jurisprudence, in the present case, three different Federal Circuit judges reached the opposite conclusion from the *Pfizer* panel about the obviousness of the salt formation, even though Sanofi had merely chosen from among *the exact same list of 53 acids* at issue in *Pfizer*. See, *e.g.*, App., *infra*, 70a, 73a; see also note 2, *supra*. The difference between the two cases is explained not by their facts (which as regards salt formation were quite similar), but by the legal analysis. The panel in this case relied on what the *Pfizer* panel and the PTO have disclaimed: the unpredictability of the chemical reactions. What is more, three of the Federal Circuit's judges wanted the court to rehear *Pfizer* en banc. They criticized *Pfizer*'s use of an "obvious to try" analysis (even though by then *KSR* had endorsed it) and emphasized the supposedly "unexpected properties" of the patented substance. See 488 F.3d 1377, 1379-1384 (2007). Two of those dissenting three judges were panelists in this case.

Those judges' views have tended to prevail in other cases as well. For example, the author of the opinion below decided in another recent case that a patented drug delivery formulation was likely not "obvious to try" under *KSR*, even though it was within a finite universe of known options suggested

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to try," see 72 FED. REG. at 57532; *In re Kubin*, 561 F.3d 1351, 1358-1361 (Fed. Cir. 2009), but *Kubin* does not present the question whether a showing of any unpredictability negates obviousness based on "obvious to try." See 561 F.3d at 1360 ("[T]his record shows that one of skill in this advanced art would find these claimed 'results' profoundly 'predictable.'").

by the prior art, because "the results obtainable from" any one "selected component" were not predictable. *Abbott Labs.* v. *Sandoz, Inc.*, 544 F.3d 1341, 1350-1351 (Fed. Cir.), reh'g denied (Feb. 23, 2009).[7] And a panel led by another of the judges who decided the present case approved a district court's pre-*KSR* dictum to the effect that "unexpected results" could rebut a *prima facie* case of obviousness. See *Takeda Chem. Indus., Ltd.* v. *Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1354, 1359, 1360-1362 (Fed. Cir.), reh'g denied (Sept. 27, 2007), cert. denied, 128 S. Ct. 1739 (2008).

Thus while at least one Federal Circuit panel (and the PTO) have focused correctly on the obviousness of the path followed to reach a result, most of the others have focused on whether the properties of the result could have been precisely predicted in advance, implicitly assuming that *KSR* does not apply when there is such unpredictability. The approach seems to depend in large part on who the panelists are. And yet the Federal Circuit (in stark contrast to the PTO) is making no effort to harmonize its rulings with each other and with *KSR*.

The result is enormous uncertainty in an area of the law in which certainty is crucial. Companies make research, development, investment, and marketing decisions based on predictions about whether potential inventions will qualify for patents in the PTO, and whether issued patents will survive court

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[7] This rationale was advanced by Judge Newman's "Opinion for the court," *id.* at 1343. One judge dissented. See *id.* at 1378. The third concurred in the judgment, but without joining this section of the opinion or authoring another.

challenges. When the Federal Circuit's behavior is not only inconsistent but regularly in conflict with that of the PTO, it becomes impossible to make reliable predictions. This kind of uncertainty is extraordinarily harmful to consumers as well as companies. For example, in the pharmaceutical industry, such uncertainty emboldens brand companies to seek to enforce questionable patents and deters potential competitors from challenging those efforts.

D. The Federal Circuit's subsidiary justifications for upholding the patent – namely that Sanofi had spent tens of millions of dollars on developing the racemate *before* deciding to separate the enantiomers, and that separating the enantiomers was time- and labor-intensive, see page 10, *supra* – are also misplaced and will work great mischief if left in place. First of all, "sweat of the brow" is not a criterion for patentability. See 35 U.S.C. § 103(a) ("Patentability shall not be negatived by the manner in which the invention was made."); *Compton*, 453 F.2d at 42 ("Neither is the amount of time spent by Compton in devising the method a controlling factor."); cf. *Feist Publ'ns, Inc.* v. *Rural Tel. Serv. Co.*, 499 U.S. 340, 359-360 (1991). Were it otherwise, many laborious but unimaginative undertakings that would "occur in the ordinary course" and do not represent "real innovation," 550 U.S. at 419, would qualify for a patent.

What is more, the investment that impressed the lower courts mostly took place *before* the Aubert patents and Sanofi's public promotion of PCR4099 – the very prior art disclosures against which the later patent must be judged. Sanofi's investment, in other words, was protected by – and rewarded with – the

earlier patents. To reward Sanofi for its *earlier* investment by upholding a *later* patent on an inexorable minor advance is to violate the patent bargain in precisely the way that *KSR* warned against.[8]

II. The Question Presented Arises Constantly and Is Tremendously Important

The patent statute covers (among several other categories of invention) "new and useful . . . composition[s] of matter." 35 U.S.C. § 101. But it is rarely if ever possible to know all of the properties of a new composition of matter before it is created. See, *e.g.*, CHISUM ON PATENTS § 5.04[6], at 5-472 (2008) ("Because of the unpredictable nature of chemical reactions, a newly-synthesized compound may be very similar in structure to known and existing compounds and yet exhibit very different properties."). In fields devoted to generating new compositions of matter, workers of ordinary skill conduct experiments every day in the belief that they are reasonably likely to obtain a useful result – even though they cannot

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[8] Contrary to what the Federal Circuit apparently assumed, it is not at all clear that a patent should be available as the end product of any successful research and development work. An influential academic account offers the insight that a patent is designed to claim a space in which, for a limited time, the patentee alone has the right to "prospect" by developing "known technological possibilit[ies]" within that space. Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J. L. & ECON. 265, 266 (1977). A patent, in other words, can be seen as an initial condition for, not the culmination of, a research and development effort. The '596 patent appropriately ensured that only Sanofi could work with PCR4099, but that does not mean that all of the additional work Sanofi did with PCR4099 in turn should qualify for a new patent.

perfectly predict what the result will be. If any degree of unpredictability or unexpectedness sufficed to impart patentability, then virtually every new substance could be removed from the public domain for at least 20 years, even when creating or isolating it was the obvious thing to do.

Accordingly, the question presented – which the leading treatise describes as a "key problem" in patent law, CHISUM, *supra*, § 5.04[6], at 5-472 – is critical to the public's ability to access the fruits of fields like pharmacology, biotechnology, industrial and agricultural chemistry, and the like. See, *e.g.*, *Pfizer*, 480 F.3d at 1367 (recognizing potential impact on the pharmaceutical industry of an obviousness standard based on "obvious to try"); Jonathan J. Darrow, *The Patentability of Enantiomers: Implications for the Pharmaceutical Industry*, 2007 STAN. TECH. L. REV. 2, 3 & n.20 (2007) (noting significance to chemical industries generally of patentability of chiral molecules); Note, *Putting the Brakes on Drugs: The Impact of KSR v. Teleflex on Pharmaceutical Patenting Strategies*, 42 GA. L. REV. 905 (2008); Note, *"Obvious To Try": A Proper Patentability Standard in the Pharmaceutical Arts?*, 76 FORDHAM L. REV. 2625 (2008). The decision below, and others like it, create an incentive to game the system by engaging in what might be called the inventing of patents rather than the patenting of inventions. And when, as in this case and many others, the product with the supposedly "unpredicted" features is in a category to which one already has exclusive rights, the only effect of the additional patent is gratuitously to extend a monopoly that was supposed to be of limited duration.

This phenomenon is of particular concern in the pharmaceutical industry, because it allows companies with patents on brand-name drugs to delay consumers' access to generic drugs, which not only are themselves cheaper but also provide competition that often reduces the prices of brand-name drugs. Limiting competition in turn has adverse effects on the overall cost and availability of heath care. There will always be new methods of modifying drugs or isolating promising variants, and it will never be possible to predict all of the properties of a new substance. The Federal Circuit's decision, by providing a roadmap for pharmaceutical patent-holders seeking to extend monopolies that no longer serve any social purpose, contributes to the needless escalation of already soaring health-care costs.

Cases presenting this issue abound. In the past three years alone, the Federal Circuit has issued published – but inconsistent – decisions in at least seven such cases.[9] Moreover, the specific fact pattern presented here (an enantiomer patented over the racemic mixture) is a good vehicle for examining the issue. For one thing, it neatly illustrates the question presented. In fact, this is the paradigmatic (though far from only) context in which the question presented arises. See Darrow, *The Patentability of Enantiomers*, *supra*, at 37-51. And the pertinent scientific principles here are limited in number and

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[9] In addition to this case, see *Abbott Labs.*, *supra*; *Takeda Chem.*, *supra*; *Pfizer*, *supra*; *Alza*, *supra*; *Aventis Pharma Deutschland GmbH* v. *Lupin, Ltd.*, 499 F.3d 1293, 1301-1303 (Fed. Cir. 2007), reh'g denied (Dec. 3, 2007); *Procter & Gamble Co.* v. *Teva Pharms. USA, Inc.*, 566 F.3d 989, 994-998 (Fed. Cir. 2009).

relatively accessible, especially in comparison to other pharmacology and biotechnology cases.

Finally, litigation over this fact pattern has become quite common, giving this Court the benefit (especially valuable in a technical area) of reference points from other courts' reactions to similar cases. See, *e.g.*, *Aventis Pharma Deutschland GmbH* v. *Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007); *Forest Labs., Inc.* v. *Ivax Pharms., Inc.*, 501 F.3d 1263 (Fed. Cir. 2007); *Pfizer Inc.* v. *Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 516-519 (D. Del. 2005); *Ortho-McNeil Pharm., Inc.* v. *Mylan Labs., Inc.*, 348 F. Supp. 2d 713, 749-755 (N.D.W. Va. 2004); *Emory Univ.* v. *Glaxo Wellcome Inc.*, 44 U.S.P.Q.2d 1407, 1414 (N.D. Ga. 1997).

In sum, this Court should review an approach to patentability that will "stifle, rather than promote, the progress of useful arts," *KSR*, 550 U.S. at 427. Because the Federal Circuit has shown no interest in resolving the confusion in its cases, the perception of an appellate lottery on the question presented will endure until this Court speaks. This Court should clarify that *KSR*'s guidance is not limited to cases involving mechanical combinations, but applies even when there is an element of unpredictability to the technology. This is the right case in which to do so.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted.

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JULY 2009

APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2007-1438

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO, INC., and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Plaintiffs-Appellees,

v.

APOTEX, INC. and APOTEX CORP.,

Defendants-Appellants.

Appeal from the United States District Court for the Southern District of New York in case no. 02-CV-2255, Judge Sidney H. Stein.

DECIDED: December 12, 2008

Before NEWMAN, LOURIE, and BRYSON, *Circuit Judges*.

NEWMAN, *Circuit Judge*.

This suit arose in accordance with the provisions of the Hatch-Waxman Act, codified at 35 U.S.C. § 271(e) and 21 U.S.C. § 355(j). The patent at issue is

United States Patent no. 4,847,265 (the '265 patent), owned by Sanofi-Synthelabo and related companies (collectively "Sanofi"), and covers the pharmaceutical product having the common name clopidogrel bisulfate and the brand name Plavix®. The product has the property of inhibiting the aggregation of blood platelets, and is used to treat or prevent blood-thrombotic events such as heart attacks and strokes. We affirm the district court's ruling sustaining patent validity.

BACKGROUND

Clopidogrel is the common name of the dextro-rotatory isomer of the chemical compound named methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate. Claim 3 of the patent is in suit:

> 3. Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-)thienopyridyl)(2-chlorophenyl)-acetate sub-stantially separated from the levo-rotatory isomer.

The '265 patent was issued on July 11, 1989, with priority from an application first filed in France in 1987. Approval of the product by the United States Food and Drug Administration (FDA) was received in 1998.

Apotex, Inc. filed an Abbreviated New Drug Application (ANDA)[1] in November 2001 for FDA ap-

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[1] Federal approval of a generic counterpart of a previously approved drug pursuant to an ANDA requires showing that the generic product is the same as the approved product; evidence

proval to sell clopidogrel bisulfate, stating, pursuant to 21 U.S.C. §355(j)(2)(A)(vii)(IV), that it believed the '265 patent to be invalid. Such "paragraph IV certification" is defined as an act of infringement for litigation purposes, 35 U.S.C. §271(e), in order to facilitate pre-marketing legal challenge by the producer of a generic form of a patented pharmaceutical product. In accordance with the statutory procedures Sanofi duly filed suit for infringement, and Apotex counterclaimed that the '265 patent is invalid on several grounds and unenforceable. The suit initiated a thirty-month stay of FDA approval of Apotex's ANDA, as provided by 21 U.S.C. §355(j)(5)(B)(iii). A proposed settlement was not achieved, the statutory stay expired, the FDA approved the Apotex ANDA, and Apotex commenced sale of its generic clopidogrel bisulfate product on August 8, 2006. Sanofi then moved in the district court for a preliminary injunction, asking that Apotex be enjoined from marketing its infringing product while the litigation was pending, noting that infringement was conceded by Apotex.

The district court found that Sanofi was likely to succeed on the merits of the validity and enforceability of the '265 patent, and that the equitable factors of the balance of harms, the probability of irreparable harm, and the various public interests, favored granting the injunction. *Sanofi-Synthelabo v. Apotex Inc.*, 488 F. Supp. 2d 317, 350 (S.D.N.Y. 2006) ("*Sanofi I*"). This court affirmed the district court's rulings, while explaining that the record on the

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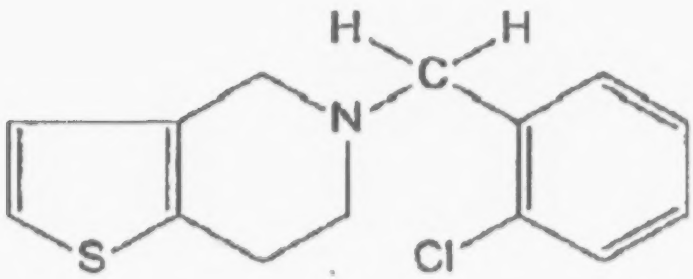
of safety and efficacy of the generic product is not required. *See* 21 U.S.C. §§ 355(j)(2)(A) and 355(b)(1).

substantive issues was necessarily incomplete and that the district court could review all aspects at trial. *See Sanofi-Synthelabo v. Apotex Inc.*, 470 F.3d 1368, 1374-84 (Fed. Cir. 2006) ("*Sanofi II*") (holding that the patentee was likely to succeed on the merits, and that the balance of hardships and public interest supported the injunction). A bench trial was held from January 22 to February 15, 2007, following which the district court ruled that the '265 patent is valid and enforceable. *Sanofi-Synthelabo v. Apotex Inc.*, 492 F. Supp. 2d 353, 397 (S.D.N.Y. 2007) ("*Sanofi III*").

This appeal is focused on the question of patentability of this dextrorotatory isomer in view of its known racemate described in earlier Sanofi patents, specifically, Sanofi's United States Patent No. 4,529,596 (the '596 patent) and Canadian Patent No. 1,194,875 (the '875 patent). Both reference patents are derived from the same French priority filing and are prior art against the '265 patent.

The activities that led to the product in suit are discussed in the earlier opinions, and are summarized as relevant herein: In 1972 Sanofi scientists were seeking products that might have improved anti-inflammatory properties, and in the course of this work discovered that certain compounds of the class known as thienopyridines (compounds having a thiene ring fused to a pyridine ring) have the property of inhibiting blood platelet aggregation. Sanofi scientists, led by Dr. Jean-Pierre Maffrand, pursued this direction of research. The record states that they initially synthesized and evaluated several hundred chemical modifications and derivatives of

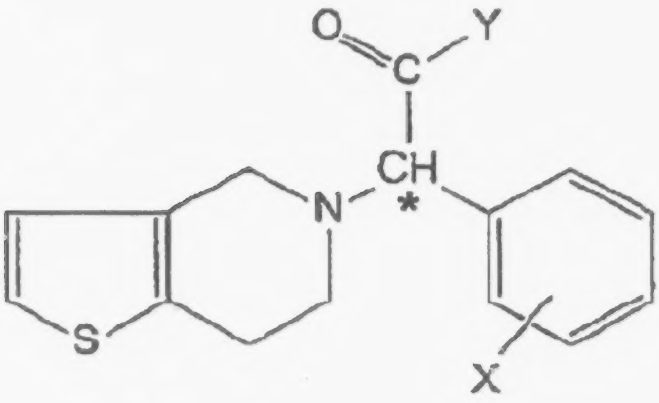
thienopyridines, seeking optimum anti-platelet aggregation properties with minimal undesirable effects. They eventually selected for development the compound having the following structural formula:



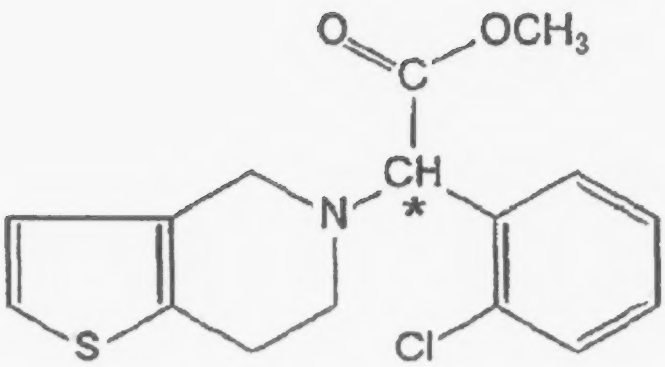
Sanofi gave this compound the common name "ticlopidine." After lengthy development, including animal and human trials, in 1991 ticlopidine was approved in the United States for use as an anti-thrombotic agent. This approval, however, was accompanied by required warnings concerning possible adverse effects, for reports had been received of rarely occurring but serious blood disorders, neutropenia and thrombotic thrombocytopenic purpura, associated with prolonged usage of ticlopidine. Thus Sanofi continued its search for a product that would have the therapeutic benefits of ticlopidine but without the adverse properties.

Sanofi synthesized and evaluated several hundred additional thienopyridine derivatives, including a class of compounds having the following general structure, wherein one of the hydrogen atoms on the bridge carbon atom (marked with an asterisk), is

replaced with an ester, carboxylic acid, or amide group. This class is the subject of the '596 patent (and the counterpart Canadian '875 patent), and is shown as follows:



X and Y can be any of a number of substituents, as identified in the patents; the district court found that there are thirty-seven possibilities for X and 1710 choices for Y. The patents state that compounds of this class exhibit good anti-platelet aggregation properties and are well tolerated. Focusing on the '596 patent, the specification includes twenty-one examples of specific compounds, including a compound designated as PCR 4099, which Sanofi synthesized in July 1980. In PCR 4099 the substituent attached to the bridge carbon is the methyl ester group (-$COOCH_3$), and X is chlorine in the 2-position, as follows:



This compound has the chemical name methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thienopyridyl)(2-chlorophenyl)-acetate, with the acronym MATTPCA. PCR 4099 as the hydrochloride salt was selected for commercial development as a potential replacement for ticlopidine in light of its improved platelet inhibition and toxicity profile.

However, PCR 4099 still raised toxicity concerns, for at very high doses it caused convulsions in laboratory animals. Thus the research efforts continued, concurrently with the clinical and commercial development of PCR 4099. Sanofi states that about 1500 compounds in this general class were synthesized, of which about 600, including PCR 4099, were chiral thienopyridines. "Chiral" is defined as "describ[ing] asymmetric molecules that are mirror images of each other, i.e., they are related like right and left hands. Such molecules are also called enantiomers and are characterized by optical activity." Richard J. Lewis, Sr., *Hawley's Condensed Chemical Dictionary* 270 (15th ed. 2007).

Enantiomers are spatial isomers, also called stereoisomers, wherein the isomeric compounds have the same chemical formula and the same chemical structure, but differ in their orientation in three-dimensional space. Such stereoisomers can exist for all molecules that contain an asymmetric carbon atom. An "asymmetric carbon" is a carbon atom to which four different substituents are attached, whereby, due to the tetrahedral structure of carbon bonds in three dimensions, the spatial orientation of substituents attached to a carbon atom varies. When there is only one asymmetric carbon atom in the molecule and thus only two stereoisomers, these isomers are called enantiomers.

Enantiomers are identified and distinguished by their optical characteristics when a purified solution of the separated isomers is exposed to plane-polarized light. One enantiomer will rotate plane-polarized light to the right (and thus is called the dextrorotatory or *d*- or (+) isomer), and the other rotates plane-polarized light to the left (called the levorotatory or *l*- or (-) isomer). For the compounds here at issue, the asymmetric carbon is at the bridge between the thienopyridine and the benzene components of the molecule, as marked with an asterisk in the drawings shown *ante*. Enantiomers generally are formed in equal amounts, to produce what is called a racemate; the racemate is optically neutral.

In the district court, experts for both sides explained the difficulty of separating enantiomers, for they are identical except for the spatial arrangement at one of the carbon atoms. Sanofi

scientists had previously separated the enantiomers of two thienopyridines, and had found that the separated enantiomers showed no advantage over the racemates. The first such separation was conducted in 1978 for a compound designated PCR 1033, which had a methyl group in place of one of the hydrogen atoms on the bridge carbon of ticlopidine, and whose maleate salt was found to be more potent than ticlopidine in antiplatelet activity but had undesirable side effects. On separation, it was found that one of the enantiomers of PCR 1033 was more biologically active but also more neurotoxic than the racemate. Thus, separation offered no benefit for PCR 1033.

About three years later, Sanofi separated the enantiomers of a compound designated PCR 3233, which had an ethyl group on the bridge carbon, and was more effective in antiplatelet activity than ticlopidine. However, neither of the separated enantiomers differed in activity from the racemate, and thus separation offered no benefit for PCR 3233. Sanofi witnesses testified to their belief that there was no advantage to separation of the enantiomers of thienopyridines, and no other racemates were separated until, in November 1985, Dr. Maffrand decided to study the enantiomers of PCR 4099.

The separation for PCR 4099 was assigned to Mr. Alain Badorc, the chemist who had separated the enantiomers of PCR 1033 and 3233. It was explained in the district court that such separations are complex and time-consuming, for enantiomers are identical except for the spatial orientation about one carbon atom, and tend to have identical or almost

identical chemical and physical properties. The district court received testimony that although the chemical literature shows at least ten separation techniques that might be tried, it cannot be known in advance which, if any, technique might work.

The record shows five months of experimentation by Mr. Badorc, and eventually the successful separation using a technique called diastereomeric salt formation. This procedure, which originated with Louis Pasteur, is based on the trial of diverse salt-forming compositions and conditions, in the hope of coming upon a lucky combination of reagents that will preferentially select one of the enantiomers and crystallize from the solution in optically pure form. In Mr. Badorc's successful experiment, he prepared thirty compositions of PCR 4099 and various resolving acids at various concentrations and in various solvents, and after about one month crystals formed in the composition containing (+)camphor-sulfonic acid and PCR 4099 in a 4:10 ratio, dissolved in acetone. This combination eventually yielded the pure levorotatory enantiomer, and isolation of the pure dextrorotatory enantiomer followed, as discussed by the district court in *Sanofi III*, 492 F. Supp. 2d at 372-73.

Sanofi then determined the biological properties of the enantiomers of PCR 4099, and found that they had the rare characteristic of "absolute stereo-selectivity": the dextrorotatory enantiomer provided all of the favorable antiplatelet activity but with no significant neurotoxicity, while the levorotatory enantiomer produced no antiplatelet activity but virtually all of the neurotoxicity. The experts for both

sides agreed that while it was generally known that enantiomers can exhibit different biological activity, this degree and kind of stereoselectivity is rare, and could not have been predicted. The experts explained that in the usual case, if one enantiomer is more biologically active than the other, that activity includes the adverse as well as the beneficial properties.

In view of these results, in April 1987 Sanofi terminated commercial development of the racemate PCR 4099, which had been proceeding since 1980 and had reached Phase I human trials at a cost stated to be tens of millions of dollars. More years of development ensued for the dextrorotatory enantiomer, to which Sanofi gave the common name "clopidogrel." Sanofi also found that the hydrochloride salt, which had been suitable for processing and tabletting the racemate PRC 4099, was not suitable for clopidogrel. After further research, Sanofi found that the hydrogen sulfate salt (also called the bisulfate) was suitable for tabletting. FDA approval of clopidogrel bisulfate was achieved in the United States in 1998, allowing introduction of the product Plavix®.

Sanofi filed a patent application directed to clopidogrel and certain salts and pharmaceutical compositions, in France on February 17, 1987 and then in the United States and other countries. The United States patent is the '265 patent in suit. The '265 specification explains that the racemate of the same chemical formula was described in the earlier French '247 patent, which corresponds to the earlier U.S. '596 patent. The '265 patent discusses the unusual stereoselectivity of the biological properties as be-

tween the dextrorotatory and the levorotatory enantiomers. The United States patent examiner, who had also examined the '596 patent, allowed the claims after requiring that the '265 claims make clear that the dextro- and levo-enantiomers are "substantially separated."

Apotex stipulated that claim 3 of the '265 patent is literally infringed by its product. The district court, after full trial including extensive expert testimony provided by both sides, ruled that claim 3 is valid and enforceable. Apotex appeals the court's rulings on the issues of anticipation and obviousness; the rulings in Sanofi's favor on the issues of unenforceability and double patenting are not appealed.

ANTICIPATION

Claimed subject matter is "anticipated" when it is not new; that is, when it was previously known. Invalidation on this ground requires that every element and limitation of the claim was previously described in a single prior art reference, either expressly or inherently, so as to place a person of ordinary skill in possession of the invention. *See Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003); *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1267-69 (Fed. Cir. 1991). An anticipating reference must be enabling; that is, the description must be such that a person of ordinary skill in the field of the invention can practice the subject matter based on the reference, without undue experimentation. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1306-07 (Fed. Cir. 2006); *Elan Pharms., Inc. v.*

Mayo Found. for Med. Educ. & Research, 346 F.3d 1051, 1054 (Fed. Cir. 2003). Anticipation is a question of fact, and the district court's finding of this issue is reviewed for clear error. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 347 F.3d 1367, 1369 (Fed. Cir. 2003).

A

The district court identified the limitations stated in claim 3 of the '265 patent as (1) the bisulfate salt of (2) the dextrorotatory enantiomer of (3) the compound MATTPCA (4) substantially separated from the levorotatory enantiomer. The references on which Apotex relied were the '596 patent or its Canadian '875 counterpart. Apotex argued that either reference not only shows the racemate PCR 4099, but also its addition salts and enantiomeric forms. The district court discussed that these references show PCR 4099 only as the racemate, and do not show the separated enantiomer or the bisulfate salt thereof. The district court found that although the racemate is in the prior art, the dextrorotatory enantiomer and salt in claim 3 of the '265 patent are not described, either explicitly or inherently, in any reference.

The court heard expert witnesses for both sides, who agreed that persons of ordinary skill in this field would have known that compounds that contain an asymmetric carbon atom have enantiomers. The '596 specification states: "These compounds having an asymmetrical carbon may exist in the form of two enantiomers. The invention relates both to each enantiomer and their mixture." '596 patent, col. 1, lines 39-41. However, as the witnesses agreed, all of

the compounds in the '596 patent are racemates, and neither the twenty-one specific examples nor any other part of the specification shows their separation into enantiomers. The district court reasoned that a person of ordinary skill in the field of the invention would not have been guided to either the dextrorotatory enantiomer of PCR 4099 or its bisulfate salt.

Apotex argues that the district court erred in law, and that it suffices that the reference shows the specific racemate PCR 4099 and states that the compounds in the reference have enantiomers and that the enantiomers are included in the invention. Apotex states that the separation of enantiomers is routine, even if time-consuming or requiring some experimentation, and thus that that the separation need not have been performed or described in the reference. Apotex states that the properties of the enantiomers of PCR 4099 are inherently and necessarily present in its known racemate, such that when the enantiomers are separated the previously observed properties are "immediately recognized" in one or the other enantiomer.

Apotex stresses that the '596 patent's Example 1 is specific to PCR 4099, and the '596 claims refer to "addition salts with pharmaceutically acceptable mineral or organic acids" and "both enantiomeric forms or their mixture." The counterpart Canadian '875 patent states that when the desired structure is obtained it "is isolated and, if desired, its enantiomers are separated and/or it is salified by mineral or organic acid action." Apotex concedes that the references do not show any separated

enantiomers or describe how to separate them, but argues that such detail is not required because persons of ordinary skill would know the existing techniques for separating enantiomers. Apotex thus argues that the dextrorotatory enantiomer of MATTPCA cannot be deemed novel, as a matter of law. However, as the district court recognized, that is not the correct view of the law of anticipation, which requires the specific description as well as enablement of the subject matter at issue. To anticipate, the reference "must not only disclose all elements of the claim within the four corners of the document, but must also disclose those elements 'arranged as in the claim.'" *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008) (quoting *Connell v. Sears, Roebuck & Co.*, 722 F.2d 1542, 1548 (Fed. Cir. 1983)); *see also, e.g., In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) ("[The] reference must clearly and unequivocally disclose the claimed [invention] or direct those skilled in the art to the [invention] without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings of the cited reference" (emphasis in original)).

The district court analyzed the question as whether a generic disclosure necessarily anticipates everything within the genus, and recognized that the answer depends on the factual aspects of the specific disclosure and the particular products at issue. *See, e.g., Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006) ("It is well established that the disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus."). In *In re Ruschig*, 343 F.2d 965, 974

(CCPA 1965), the court declined to find the disclosed genus anticipatory of everything within its scope, when the description of the genus would not lead a person of ordinary skill to a "small recognizable class with common properties." In this case the district court correctly declined to find that the references' general statements that these compounds consist of enantiomers constituted an anticipating disclosure of the separated dextrorotatory enantiomer of PCR 4099.

The district court discussed the cases on which Apotex particularly relied: *In re Petering*, 301 F.2d 676 (CCPA 1962), and *In re Schaumann*, 572 F.2d 312 (CCPA 1978). The court pointed out that in *Petering* and *Schaumann* the generic disclosure in the reference identified "specific preferences," which were met by the later-described species. We discern no clear error in the district court's finding that the references herein contained no such specific preferences. PCR 4099 is shown in the references as one of several compounds with desirable biological properties, but the district court did not clearly err in finding that the reference disclosure would not have led one of ordinary skill to recognize either an explicit or an inherent disclosure of its dextrorotatory enantiomer, as well as the bisulfate salt.

Apotex also relies on *In re Adamson*, 275 F.2d 952 (CCPA 1960), where the court held that although the reference did not state that the disclosed compound was a racemate, it would have been known to one of ordinary skill that synthetically produced chiral compounds are racemic. Sanofi does not dispute this statement of stereochemistry, but points out that

knowledge of the existence of enantiomers is not a description of a specific enantiomer "substantially separated" from the other, as in claim 3 of the '265 patent. The district court cited *In re May*, 574 F.2d 1082 (CCPA 1978), which is explicit that "the novelty of an optical isomer is not negated by the prior art disclosure of its racemate." *Id.* at 1090. Also, *Adamson* and *May* were addressing rejections for obviousness, and neither case stated or suggested a previously unseparated and unknown enantiomer might be deemed anticipated by the known racemate.

The district court did not clearly err in finding that the statements in the '596 patent and its Canadian counterpart that the products therein consist of enantiomers are not a description of the specific dextrorotatory enantiomer clopidogrel or a suggestion of its unusual stereospecific properties. The knowledge that enantiomers may be separated is not "anticipation" of a specific enantiomer that has not been separated, identified, and characterized. The district court correctly held that neither the '596 patent nor its Canadian counterpart contains an anticipating disclosure of the subject matter of claim 3 of the '265 patent.

B

The parties also debated the question of enablement with respect to anticipation. The district court found that the asserted references are not enabling, for they contain no guidance as to how to separate the enantiomers of PCR 4099. Based on the evidence adduced at trial, the court concluded that absent

such guidance, undue experimentation would be required.

Apotex argues that it is entitled to a presumption of enablement because the asserted references are patents, which are presumed to be enabling because they are presumed valid, citing *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 2003) ("We hold that an accused infringer should be similarly entitled to have the district court presume the enablement of unclaimed (and claimed) material in a prior art patent defendant asserts against a plaintiff."). Apotex argues that the presumption should be particularly strong here, because the prior art patents belong to Sanofi. Thus Apotex argues that the general statements in the reference patents concerning enantiomers are presumptively enabling of the separate enantiomers of PCR 4099. Apotex states that it is irrelevant whether the separation of this specific enantiomer is shown in the references, because a person of ordinary skill in this field would know all of the existing techniques for separating stereoisomers, and would presumptively succeed in this particular separation. Apotex points out that the method that was eventually used by Sanofi was a well-known method, even if it involved some experimentation.

Any presumption of enablement of prior art does not exclude consideration of whether undue experimentation would be required to achieve enablement. *See, e.g., Elan Pharms.*, 346 F.3d at 1054 (the reference must teach how to carry out the invention without undue experimentation). The factors relevant to whether experimentation is undue are

discussed in, e.g., *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988), and include the quantity of experimentation that was actually needed, the amount of guidance provided in the reference, the presence or absence of actual examples of the experimental procedure, the state of the knowledge already available concerning the subject matter at issue, and the predictability or unpredictability in the specific area of science or technology. The '596 patent reference states only that "if desired, its enantiomers are separated," and similarly for the Canadian counterpart. The district court found that these references contain no description of how to separate the enantiomers of PCR 4099, and that "[d]iscovering which method and what combination of variables is required is sufficiently arduous and uncertain as to require undue experimentation, even by one skilled in the relevant art." *Sanofi III*, 492 F. Supp. 2d at 387. This finding has not been shown to be clearly erroneous. In *Forest Laboratories, Inc. v. Ivax Pharmaceuticals, Inc.*, 501 F.3d 1263 (Fed. Cir. 2007), this court recognized the known difficulty of separating enantiomers and the unpredictability of their properties, and held that a reference that stated that a compound has enantiomers did not enable the separation of those enantiomers, where the reference did not teach how to obtain the enantiomer. *Id.* at 1268-69. We discern no clear error in the district court's finding herein that the reference patents would not have enabled a person of ordinary skill to obtain clopidogrel substantially separated from the levorotatory enantiomer.

The district court's ruling that claim 3 of the '265 patent is not invalid for anticipation is affirmed.

OBVIOUSNESS

The determination of obviousness is a matter of law based on findings of underlying fact, wherein the factors identified in *Graham v. John Deere Co.*, 383 U.S. 1 (1966), guide the inquiry:

> Under §103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

Id. at 17-18.

The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim. *See KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1734 (2007); *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448 (Fed. Cir. 1984). For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination. *See In re Sullivan*, 498 F.3d 1345, 1353 (Fed. Cir. 2007); *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963). Precedent establishes the analytical procedure whereby a close structural similarity between a new chemical compound and prior art compounds is generally deemed to create a prima facie case of obviousness, shifting

to the patentee the burden of coming forward with evidence of nonobviousness. The evidence may take various forms, as relevant in the particular case. *See, e.g., Takeda Chem. Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1358, 1362-63 (Fed. Cir. 2007) (prima facie case depends on whether the prior art provided a suggestion or reason to choose a specific lead compound for modification, or to make the specific modification of the compound at issue); *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (same). The ultimate determination is made in the context of the *Graham* factors, with the challenger having the ultimate burden of proving invalidity by clear and convincing evidence. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007).

The district court assumed that Apotex had made a prima facie case of obviousness based on the reference patents' disclosure of the PCR 4099 racemate, the statements in the patents concerning enantiomers, and the general knowledge that enantiomers may be separated and may differ from each other in biological properties. Upon consideration of the *Graham* factors, the court held that the unpredictable and unusual properties of the dextrorotatory enantiomer and the therapeutic advantages thereby provided, weighed in favor of nonobviousness, and that Apotex had not met its burden of establishing otherwise.

Apotex argues that the recognition in the prior art that PCR 4099 is composed of enantiomers outweighs the effect of any unexpected or unpredictable properties of the separated dextrorotatory enan-

tiomer. Apotex asserts that Sanofi's previous selection of PCR 4099 as a promising replacement for ticlopidine would have led a skilled artisan to start with PCR 4099 as a lead compound for further research. Apotex states that it was well known that enantiomers can have different levels of biological activity even if the exact allocation of properties is unpredictable, thereby rendering it obvious to separate the enantiomers and determine their properties. Apotex contends that the only features of clopidogrel bisulfate arguably not explicit in the prior art – the separation of the dextro- from the levorotatory enantiomer and its preparation as a bisulfate salt – required no more than well-known chemical techniques. Apotex cites known examples of other chiral compounds that exhibit stereoselectivity, and argues that the general knowledge that a favorable allocation of properties is possible suffices to render the separation obvious to a person of ordinary skill.

Apotex thus argues that there was motivation to separate the enantiomers of PCR 4099, and that a person of ordinary skill in the field would have been able to do so using known procedures, even if some experimentation was required, and then, upon separation of the enantiomers, routine testing would have revealed the favorable allocation of properties in the dextrorotatory isomer. Apotex asserts that it is not material that this allocation was unknown in advance and unpredictable, and that what matters is whether a person of ordinary skill would have had a reasonable probability of success in the separation and evaluation of the enantiomer, citing *Pfizer*, 480 F.3d at 1364, wherein this court observed that "case law is clear that obviousness cannot be avoided sim-

ply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."

Sanofi responds by challenging Apotex's view of the law, and citing the evidence on the factual premises of these arguments. At trial the expert witnesses for both sides agreed that a person of ordinary skill in this field in the mid-1980s would have known that enantiomers can exhibit different biological activities. However, the experts also agreed that it was not predictable whether such differences, if any, would be weak, moderate, or strong, or how they would be manifested. The experts agreed that no known scientific principle allows prediction of the degree to which stereoisomers will exhibit different levels of therapeutic activity and toxicity. The experts agreed that weak stereoselectivity of biological properties is more common than strong stereoselectivity, and that absolute stereoselectivity is rare. Sanofi witnesses testified as to the research team's belief, based on the earlier separations of two other thienopyridines, that separation of enantiomers was unlikely to be productive. Apotex's expert, when asked whether one could predict in advance the therapeutic and toxic properties of the enantiomers, stated: "No. I certainly don't believe you could predict that without separating them and trying it. I can't imagine anybody presuming anything else." The experts also agreed that activity and toxicity were more likely to be positively correlated, such that a reduction in toxicity would be expected also to reduce the beneficial activity. Witnesses also explained that it was known that for compounds whose biological activity is delivered

through metabolism within the body, the acid environment in the stomach or other metabolic processes often restores the racemic state, thereby removing any potential benefit of a separated enantiomer. On the basis of this trial evidence, the district court found that a person of ordinary skill in this field would not reasonably have predicted that the dextrorotatory enantiomer would provide all of the antiplatelet activity and none of the adverse neurotoxicity. Clear error has not been shown in this finding, and in the conclusion of nonobviousness based thereon. *See Papesch*, 315 F.2d at 391 (a chemical compound and its properties are inseparable).

The district court also discussed the evidence concerning the process of separating the enantiomers of PCR 4099. Apotex argued that Sanofi's separation procedure was well known, and therefore that the separated components of the known racemate were obvious as a matter of law, whether or not they were deemed to have unexpected properties. The district court observed that in 1987 there were at least ten techniques that had been used to separate enantiomers, and that they all required experimentation to determine whether they could be successful for a particular compound, including choices of reagents, solvents, concentrations, temperature, and a variety of other conditions. The court observed that Pasteur's diastereomeric salt formation technique had long been described in chemistry textbooks, but that the textbooks also explain that the method is difficult and that there is no "infallible recipe" for obtaining separation.

The district court referred to the testimony of Sanofi's expert, Dr. Stephen G. Davies, who stated, in discussing the diastereomeric salt formation method, that it is difficult indeed to cause one enantiomer to crystallize out of solution while the other does not. As discussed *ante* in connection with anticipation, Mr. Badorc's eventual success came only after several failures using other known strategies for enantiomer separation. The court observed that although Sanofi had previously separated the enantiomers of two other thienopyridines, the diastereomeric salt formation method had succeeded in one case but failed in the other. The court also found that a person of ordinary skill would have recognized that it could be more difficult to separate the enantiomers of PCR 4099 than the two other compounds that Mr. Badorc had previously separated, because it would be understood by chemists that the methyl ester substituent in PCR 4099 could make it more susceptible to re-racemization, and thus resistant to successfully obtaining a separated product.

The district court found that this separation was not a simple or routine procedure and that success in separation, as well as the allocation of properties, was unpredictable. The court observed that Apotex did not cite any reference showing or suggesting any reliable method of separation for any analogous compounds. The court described the separation as a "paradigm of trial and error," *Sanofi III*, 492 F. Supp. 2d at 370, and found that "neither the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether

to investigate them and, if obtained, they could not have predicted by what method and configuration." *Id.* at 371. The court found that Sanofi's expenditure of tens of millions of dollars for several years of development of the racemate PCR 4099, before separating the enantiomers, also weighed against finding that separation would have been obvious. Again, Apotex has demonstrated no clear error in the extensive finding of the district court concerning the difficulty and unpredictability of the separation of these enantiomers. These unchallenged findings undermine Apotex's argument in this appeal that the separation of the enantiomers would have been obvious. Only with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties, can Apotex argue that it would have been obvious to select this particular racemate and undertake its arduous separation. The application of hindsight is inappropriate where the prior art does not suggest that this enantiomer could reasonably be expected to manifest the properties and advantages that were found for this particular dextrorotatory isomer. *See Graham*, 383 U.S. at 36 (cautioning against hindsight whereby the teachings of the invention are read into the prior art); *see also KSR v. Teleflex*, 127 S. Ct. at 1742 (recognizing "hindsight bias" and "ex post reasoning" as inappropriate in determination of obviousness).

Concerning the bisulfate salt, the district court found no evidentiary support for Apotex's argument that the '596 patent taught the dextrorotatory enantiomer of PCR 4099 as the bisulfate salt. The PCR 4099 racemate is shown in the '596 patent as the hydrochloride, not the bisulfate. The district court

observed that the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds, fifty-three of which acids had been used in FDA-approved drugs. The experts of both parties agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination is unpredictable. The district court distinguished the facts of this case from those of *Pfizer*, 480 F.3d 1348, where there was evidence that based on the prior art a person of ordinary skill would have narrowed the possible salts to only a few including the claimed besylate, whereas here Sanofi presented evidence that the prior art taught away from the use of sulfuric acid with an enantiomer, for strong acids could encourage re-racemization. Apotex has shown no clear error in the district court's finding, based on the trial evidence, that the facts distinguish this case from those in *Pfizer*.

Based on all of these findings, the district court concluded: "Whether or not it may have been 'obvious to try' separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotatory enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious." *Sanofi III*, 492 F. Supp. 2d at 392. Apotex argues that the district court applied an incorrect inquiry, and that the correct inquiry is not whether the results obtained with the separated enantiomer were unexpected, but whether it would have been obvious to separate and test the enantiomers, based on the general knowledge that

enantiomers can exhibit different properties. Apotex refers to *In re Adamson*, 295 F.2d at 955, where the CCPA held that an enantiomer would have been obvious in view of its racemate. However, the scientific facts differed from these herein, for in *Adamson* the court found that it was "particularly expected" that the specific enantiomer would have the observed properties. In contrast, as Sanofi points out, in *In re May*, 574 F.2d at 1095, the CCPA held, as to the enantiomer claimed therein, that the appellant "established a substantial record of unpredictability vis-à-vis a highly significant combination of properties."

The determination of obviousness is dependent on the facts of each case. *See Graham*, 383 U.S. at 17-18. In *Forest Laboratories*, 501 F.3d at 1269, this court affirmed that the (+) enantiomer of citalopram would not have been obvious in light of the known racemate, when it was shown that the therapeutic properties of the (+) enantiomer were unexpected. In contrast, in *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1302 (Fed. Cir. 2007), this court held that the ramipril isomer's potency was "precisely what one would expect, as compared to a mixture containing other, inert or near-inert stereoisomers." Apotex argues that *Aventis* is the closer analogy, but the evidence was directly contrary to that position. The district court entered extensive findings in this case on the unexpected and unpredictable properties of clopidogrel, and there was no contrary evidence suggesting, based on the prior art, that the stereoselective properties were "precisely what one would expect," as in *Aventis*.

Apotex also argued in the district court, and repeats on this appeal, that Sanofi separated the enantiomers only because of a possible future regulatory requirement concerning the separation of enantiomers. Apotex states that this future regulatory requirement would have alerted a person of ordinary skill to the need to separate isomers, and thus would have rendered it obvious to do so. The district court found that the sole evidence referring to this regulatory possibility, an internal Sanofi memorandum, was written several months after Sanofi had discontinued its development of the racemic PCR 4099 in favor of the dextrorotatory enantiomer; the court also cited the testimony and documentary evidence that Sanofi undertook this separation in order to study the adverse neurological effects of PCR 4099, and not because of a possible future regulatory requirement. Sanofi also points out, as the general knowledge in this field confirms, that the recognition that stereoisomers may exhibit different properties does not teach which results may ensue or how to separate any given enantiomers. We discern no error in the short shrift that the district court gave to this argument.

Apotex also argues that the district court did not take adequate account of the Supreme Court's holding in *KSR v. Teleflex* that the "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." 127 S. Ct. at 1739. Apotex states that Sanofi did no more than separate the enantiomers and determine their properties, and that the properties were predictably those of the racemate, allocated between the enantiomers. Sanofi

points out that this case does not concern a "combination of familiar elements" as in the *KSR* mechanical device made by combining known components to produce a combination having the properties of the known components. The evidence at trial well supported the finding that the result of this separation of enantiomers was unpredictable. We discern no error in the district court's implicit recognition that the principles of *KSR* do not affect the conclusion herein.

The district court thoroughly discussed the many issues and arguments raised by Apotex. We discern no error in the district court's findings that, on the state of the prior art, a person of ordinary skill would not have had the expectation that separating the enantiomers would be likely to produce an isomer having absolute stereoselectivity as to both the favorable antiplatelet activity and the unfavorable neurotoxicity. The totality of these findings, and the correct application of law, ell support the district court's conclusion that invalidity had not been established by clear and convincing evidence.

AFFIRMED

APPENDIX B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT NEW YORK

SANOFI-SYNTHELABO; SANOFI-SYNTHELABO, INC.; and BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Plaintiffs,

- against -

APOTEX, INC. and APOTEX CORP.,

Defendants.

No. 02 Civ. 2255 (SHS).

OPINION & ORDER

[June 19, 2007]

SIDNEY H. STEIN, U.S. District Judge.

After trial on the merits, this Court finds that Apotex, Inc. and Apotex Corporation (collectively, "Apotex") have failed to prove by clear and convincing evidence that U.S. Patent No. 4,847,265 is invalid or unenforceable on any of the grounds asserted. Accordingly, Sanofi-Aventis, Sanofi-Synthelabo, Inc. and Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership (collectively, "Sanofi") are entitled to permanent injunctive relief and, as shall be determined by the Court in a future proceeding, damages.

This action concerns a patent dispute between Sanofi – which invested in the research and development to patent and bring to market the drug known

as Plavix® – and Apotex, which seeks to market the generic equivalent of that drug. On the basis of the record established by the parties and the applicable law, the Court enters the following findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

FINDINGS OF FACT[1]

1. *History of this Action*

Plavix®, approved for sale in the United States by the U.S. Food and Drug Administration ("FDA") in November 1997, is prescribed for the reduction of thrombotic events such as heart attacks and strokes for patients who have recently suffered those events or who have arterial disease or acute coronary syndrome. (*See* Stipulated Statement of Facts ("Fact Stmt."), attached as Exhibit A to Joint Pretrial Order dated May 27, 2005 at ¶ 12.) The active ingredient of Plavix® is clopidogrel bisulfate. (*Id.*) Sanofi obtained a patent claiming bisulfate on July 11, 1989, naming Sanofi employees Alain Badorc and Daniel Fréhel as inventors. (*Id.* at ¶¶ 8-9.) That patent, U.S. Patent No. 4,847,265 ("the '265 patent"), claims clopidogrel bisulfate by its chemical name in Claim 3: "Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer." ('265 patent at col. 12, ll. 37-

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[1] To the extent that any findings of fact may be deemed conclusions of law, they shall also be considered conclusions of law; to the extent that any conclusions of law may be deemed findings of fact, they shall also be considered as such. *See Miller v. Fenton*, 474 U.S. 104, 113-14, 106 S. Ct. 445, 88 L. Ed. 2d 405 (1985).

41.) Sanofi-Aventis is the owner of the patent-in-suit, which expires on November 17, 2011. The foreign priority filing date of the '265 patent – the date on which Sanofi filed its earlier application for the corresponding French patent – is February 17, 1987. The '265 patent is exclusively licensed to Bristol-Myers Squibb Sanofi Pharmaceuticals Holding Partnership. (Fact Stmt. at ¶¶ 3, 13.)

Apotex sought approval from the FDA to manufacture and sell clopidogrel bisulfate tablets before the expiration of the '265 patent by filing an Abbreviated New Drug Application ("ANDA") with the FDA in November 2001. (*Id.* at ¶¶ 14-15.) In the ANDA, Apotex certified pursuant to the requirements of 21 U.S.C. § 355(j)(2)(A)(vii)(IV) that it believed the '265 patent to be invalid. (*Id.* at ¶ 16; *see also Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1344 (Fed. Cir. 2004).) Apotex was the first to file an ANDA for clopidogrel bisulfate (Decl. of Dr. Bernard Sherman, dated Aug. 16, 2006 ("Sherman Decl.") at ¶ 17), thereby securing the right to 180 days of market exclusivity provided by the Hatch-Waxman Act to the first ANDA filer to challenge a patent. *See* 21 U.S.C. § 355(j)(5)(B)(iv); *see also In re Tamoxifen Citrate Antitrust Litig.*, 429 F.3d 370, 376 (2d Cir. 2005).

In response to that ANDA filing by Apotex, Sanofi filed this litigation against Apotex on March 21, 2002 pursuant to 35 U.S.C. § 271(e), and asserted that Apotex's filing of the ANDA constituted infringement of the '265 patent, specifically Claim 3. (*See* Fact Stmt. at ¶ 17.) Apotex counterclaimed, asserting that the '265 patent is both invalid for three separate reasons and unenforceable as well.

First, Apotex alleges that the '265 patent is anticipated pursuant to 35 U.S.C. § 102(b) by an earlier patent held by Sanofi that covered a genus of chemical compounds called thienopyridines, within which clopidogrel bisulfate falls. (*See* Fourth Amended Answer and Amended Counterclaim ("Answer"), filed Nov. 17, 2006, at 3, 13.) The earlier patent, U.S. Patent No. 4,529,596 ("the '596 patent"), issued in July 1985 and expired in July 2003. (Fact Stmt. at ¶ 28.)

Second, Apotex contends pursuant to 35 U.S.C. § 103 that the subject matter claimed in the '265 patent would have been obvious to a person of ordinary skill in the art at the time the invention was made. (*See* Answer at 3, 13.)

Third, Apotex contends that the patent is invalid under the judicial doctrine of obviousness-type double patenting. (*Id.* at 6, 15.)

Finally, Apotex also asserts that the '265 patent is unenforceable on the basis of Sanofi's alleged inequitable conduct before the U.S. Patent and Trademark Office ("PTO"). The alleged conduct consists of failing to name Dr. Jean-Pierre Maffrand as an inventor, making false statements to the PTO regarding the unexpected pharmacological properties of clopidogrel bisulfate, failing to disclose relevant prior research that Sanofi had conducted on a similar chemical compound, and failing to disclose a journal article that Apotex alleges is a material prior art reference. (*Id.* at 4-6, 8-15.)

With regard to infringement, the parties have stipulated that Apotex's clopidogrel bisulfate product infringes Claim 3 of the '265 patent. (*See* May 7,

2004 Stipulation and Order; Fact Stmt. at ¶ 18.) The ensuing procedural history of this action – including an account of the extensive settlement negotiations between the parties and the consequences for this litigation – is described in detail in this Court's Opinion dated August 31, 2006; familiarity with that Opinion is assumed. *See Sanofi-Synthelabo v. Apotex Inc.*, No. 02 Civ. 2255, 2006 U.S. Dist. LEXIS 65127, at *9-16 (S.D.N.Y. Aug. 31, 2006). In brief, Apotex initiated an at-risk launch of its generic clopidogrel bisulfate product on August 8, 2006. Shortly thereafter, Sanofi moved for a preliminary injunction prohibiting Apotex from distributing its generic product. After an evidentiary hearing was held, the Court granted Sanofi's motion for preliminary injunctive relief on August 31, 2006, but denied its request for a recall of the approximately six-month supply of product that Apotex had already shipped to distributors in the United States. *Id.* at *89-91.

Apotex then moved to stay the preliminary injunction, but both this Court and the U.S. Court of Appeals for the Federal Circuit denied that motion. Apotex then appealed the order granting the preliminary injunction to the Federal Circuit, which affirmed the grant of the preliminary injunction in an opinion dated December 8, 2006. *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368 (Fed. Cir. 2006), *reh'g denied*, 2007 U.S. App. LEXIS 2807 (Fed. Cir. Jan. 19, 2007). The parties then tried the merits of this action before this Court without a jury from January 22 through February 15, 2007. That trial – as well as the evidentiary hearing held in August 2006 – adduced the following facts.

II. *Sanofi's Efforts to Develop Antiplatelet Aggregation Drugs*

A. *Ticlopidine*

In 1972, Dr. Jean-Pierre Maffrand, then a Sanofi chemist in charge of a small research team, was asked by his supervisor to synthesize compounds structurally similar to tinoridine, a drug with known anti-inflammatory properties, in an effort to discover a superior anti-inflammatory drug. (Maffrand Tr. 1570-74.)[2] Tinoridine is a member of a class of compounds known as thienopyridines. (Maffrand Tr. 1575-76.) The chemical structure of a thienopyridine is characterized by the fusion of a thiophene ring to a pyridine ring. (Maffrand Tr. 1575-76.)

During 1972 and 1973, Sanofi synthesized a number of thienopyridine compounds. (Maffrand Tr. 1573-74.) Tests on those compounds revealed that unlike tinoridine, they possessed no anti-inflammatory properties. Some of the compounds, however – one of which Sanofi named "ticlopidine" – exhibited antiplatelet aggregation activity. (Maffrand Tr. 1573-75.) Put simply, the compound helped ensure that platelets in the blood would not aggregate together as much as they otherwise would. This was an important discovery. Researchers at Sanofi were convinced that platelets play a major role in events such as myocardial infarction and brain ischemia and Dr. Maffrand and his colleagues were interested to find an antiplatelet aggregation agent that would be "[a]

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[2] References to (___ Tr. ___) refer to the page number of the trial transcript for the relevant witness. Similarly, references to (___ PI Tr. ___) refer to the page number of the transcript of the preliminary injunction hearing for the relevant witness.

better drug than aspirin." (Maffrand Tr. 1574-75.) In 1977, Sanofi obtained a patent on ticlopidine; that patent expired in 1994.

Ticlopidine was introduced as a drug in France in 1978 and in the United States in 1991, where it was marketed under the brand name "Ticlid." (Maffrand Tr. 1578-79; 1581-82.) Soon after the launch of ticlopidine in France, Sanofi became aware of rare but potentially fatal side effects associated with ticlopidine, specifically blood disorders known as neutropenia and thrombotic thrombocytopenic purpura ("TTP"). (Schneller Tr. 763, 815-16; Maffrand Tr. 1580-81.) As a result, the FDA required Ticlid to carry a "black box" warning that ticlopidine could cause life-threatening blood disorders. (Maffrand Tr. 1581.) The potential for these serious side effects meant that patients taking ticlopidine had to be clinically monitored for signs of blood disorders. (Maffrand Tr. 1581.) The sub-optimal side effect profile of ticlopidine – i.e., the risk of developing serious blood disorders – left open the need in the market for a drug that was as effective or more effective than ticlopidine, but with a lower risk of side effects.

B. *PCR 1033*

In 1975, Sanofi synthesized a thienopyridine named PCR 1033. That compound is the methyl analog of ticlopidine, which means that one of the two hydrogen atoms on the bridge carbon of a ticlopidine molecule – the carbon linking the thienopyridine and phenyl substituents – is substituted with a methyl (CH_3) group. (Maffrand Tr. 1584.) The addition of the methyl group makes the bridge carbon asymmetric. Here, some knowledge of

the basic principles of stereochemistry is required and has been best set forth by the Federal Circuit in its opinion affirming the preliminary injunction in this action:

> Stereochemistry refers to the three-dimensional spatial arrangement of a molecule's constituent atoms. Molecules that have the same chemical substituents, but different spatial arrangements, are referred to as stereoisomers. If they contain an asymmetrical carbon atom, they exist as non-superimposable mirror images of each other and are referred to as enantiomers. Enantiomers are optically active because they are capable of rotating plane-polarized light; enantiomers that rotate polarized light to the right are referred to as dextrorotatory enantiomers, or d-enantiomers; enantiomers rotating polarized light to the left are referred to as levorotatory enantiomers, or l-enantiomers. A mixture of equal amounts of both types of enantiomers is referred to as a racemic mixture, or racemate, and it exhibits no optical activity.

Sanofi-Synthelabo v. Apotex, Inc., 470 F.3d at 1372.

Unlike ticlopidine, PCR 1033 is a racemate composed of the 50:50 mixture of its enantiomers. (Maffrand Tr. 1584, 1599-1600, 1682-83.) To make PCR 1033 suitable for testing, Sanofi chemist Alain Cabrol attempted to prepare the hydrochloride salt of PCR 1033, but that effort failed. (Maffrand Tr. 1599-1600; 1699; Badorc Tr. 1810.) Instead, Sanofi prepared PCR 1033 as a maleate salt. (Maffrand Tr.

1600.) When tested, Sanofi found that PCR 1033 was a more potent antiplatelet aggregation agent than ticlopidine, but that it was also less well-tolerated than ticlopidine; side effects were observed during the initial pharmacological testing of PCR 1033 in different species. (Maffrand Tr. 1587.) Around the beginning of 1976, Sanofi ceased efforts to develop PCR 1033 because of those side effects. (Maffrand Tr. 1587.)

In 1978, Maffrand asked Alain Badorc, a Sanofi chemist, to try to obtain the enantiomers of PCR 1033. (Maffrand Tr. 1587-88; Badorc Tr. 1807.) Maffrand testified at trial that "we wanted to try our luck" to see if either enantiomer had a better ratio of antiplatelet activity to tolerance than the racemate. (Maffrand Tr. 1588.) At that time, Maffrand knew that a two-fold increase in a single enatiomer's therapeutic activity was the quantitatively best possible increase that could be attained through separation of the enantiomers of a racemate, and that such a result "is not the most frequent case." (Maffrand Tr. 1591-93; Harden Tr. 2304-06.) For that reason, Sanofi's preferred mode of searching for superior antiplatelet drugs at that time had been to modify the substituents of racemic compounds (thereby creating new compounds) – not to isolate the individual enatiomers of particular racemates – because a modified compound was the more likely path to significantly greater gains in antiplatelet activity. (Harden Tr. 2304; Maffrand Tr. 1592-94.)

Badorc successfully separated the enantiomers of PCR 1033 on his first attempt by means of a technique known as diastereomeric salt formation. (Badorc Tr. 1809; Maffrand Tr. 1702.) That method

involves combining the enantiomers of a racemic base with an enantiomerically pure chiral acid to form a diastereomeric salt (i.e., a salt with two chiral centers) in two distinct stereoconfigurations. (Davies Tr. 1934.) The resulting diastereomers, if formed, do not have identical physical properties; their different solubilities in a particular solvent, for example, may facilitate their separation. (Davies Tr. 1934-35; McClelland Tr. 1105-06.) However, the Court credits the testimony of Dr. Stephen G. Davies, an expert for Sanofi, who stated, "[t]he problem is that it is very hard to find situations where one [diastereomer] crystallizes out and the other one does not . . . . you are trying to get one to do something while leaving the other one behind." (Davies Tr. 1935-36.) If the diastereomers are successfully separated, a base is added to one of the two separated diastereomeric salts to reconstitute the original base, which is then in an enantiomerically pure form. (McClelland Tr. 1108-1109; Davies Tr. 1936-37.)

Badorc prepared the diastereomeric salts of PCR 1033 by using tartaric acid dissolved in ethanol. (Badorc Tr. 1808-09.) The levorotatory enantiomer was designated PCR 3071 and the dextrorotatory enantiomer was designated PCR 3072. (Maffrand Tr. 1598.) To facilitate further testing, Badorc prepared the hydrochloride salts of PCR 3071 and PCR 3072. (Badorc Tr. 1810.) As noted, previous efforts to prepare the hydrochloride salt of the racemate – PCR 1033 – had failed. (Maffrand Tr. 1600, 1699.) Testing on the enantiomers revealed that PCR 3071 exhibited antiplatelet activity and PCR 3072 was inactive; the active enantiomer, however, was less well tolerated than ticlopidine and was not

appropriate for administration to humans. (Maffrand 1598-99.) Sanofi discontinued the development of those enantiomers in 1981. (Maffrand Tr. 1599.)

C. *PCR 3549*

In 1978 – after Sanofi had synthesized PCR 1033 but before it had discontinued the development of PCR 3071 and PCR 3072 – Sanofi synthesized the ethyl analog of ticlopidine, which was designated PCR 3233. (Maffrand Tr. 1601-02.) Attempts to make the hydrochloride salt of PCR 3233 – an oily base – failed, but, after several failed attempts, Badorc eventually obtained its nitrate salt, which was designated PCR 3549. (Maffrand Tr. 1604; Badorc Tr. 1812.) Testing revealed that PCR 3549 was more potent than ticlopidine and better tolerated than PCR 1033, but was still less well tolerated than ticlopidine. (Maffrand Tr. 1604-05.) In November 1978, Maffrand asked Badorc to prepare the enantiomers of PCR 3549 to see if either enantiomer had a better risk/benefit profile than the racemate. (Maffrand Tr. 1605-06; Badorc Tr. 1811.) Badorc tried to separate the enantiomers of PCR 3549 using diastereomeric salt formation – the technique that he had used successfully to resolve the enantiomers of PCR 1033 – but several attempts failed. (Maffrand Tr. 1606; Badorc Tr. 1813-14.) Badorc then tried to obtain the enantiomers of PCR 3549 by a different method – chemical asymmetric synthesis. (Maffrand Tr. 1606; Badorc Tr. 1819-20.) That method involves taking a precursor compound that is enantiomerically pure and modifying the compound to obtain the desired compound, but without altering the stereochemical configuration of the precursor compound. (Davies Tr. 1932-33; Badorc Tr. 1819-20.)

At that time, Badorc believed – and he testified at trial that he still believes – that he successfully synthesized the enantiomers of PCR 3549 by that method. (Badorc Tr. 1823-24.) Badorc further testified that he confirmed his successful synthesis of the enantiomers of PCR 3549 in 1978 by measuring the rotatory power of each enantiomer, which were equal in absolute value (Badorc Tr. 1824); that result – the equal and opposite optical rotation of two products – is evidence of the presence of two enantiomers. (Davies Tr. 1981; Hendrickson Tr. 1474.) In addition, the nitrate forms of each enantiomer had equivalent melting points that were each higher than the melting point of PCR 3549. (Davies Tr. 1981.) Furthermore, "the chance is minimal, if not nonexistent," that two parallel asymmetric syntheses – such as those Badorc performed – would result in products demonstrating the same level of rotatory power and the same melting points. (Davies Tr. 1819.) The Court credits the testimony from Dr. Davies that this data provided strong evidence that Badorc had indeed obtained the enantiomers of PCR 3549 by means of asymmetric synthesis. (Davies Tr. 1981-82.)

Sanofi designated the levorotatory enantiomer PCR 3620 and the dextrorotatory enantiomer PCR 3621 and tested them for platelet aggregation inhibition activity. (Badorc Tr. 1826.) That testing showed that the platelet aggregation inhibiting activities of PCR 3620 and PCR 3621 were each comparable to PCR 3549, meaning neither improved on the racemate. (Maffrand Tr. 1615-16.) For that reason, Sanofi discontinued development of PCR 3620 and PCR 3621 and focused its efforts on PCR 3549. (Maffrand

Tr. 1616-17.) PCR 3549, however, proved to be less well-tolerated than ticlopidine at similar dosage levels, and lower doses of PCR 3549 were insufficiently therapeutic. For those reasons, Sanofi abandoned its efforts to develop PCR 3549. (Maffrand Tr. 1616-17.)

D. *PCR 4099*

Sanofi synthesized several other thienopyridines in addition to PCR 1033 and PCR 3549. After having created two carboxylic acid derivatives of ticlopidine – in 1976 and 1978, respectively – which showed no platelet inhibition, Sanofi synthesized a new compound in 1980 that had an ethyl ester ($O=C-O-CH_2-CH_3$) substituent on the bridge carbon. (Maffrand Tr. 1637-39.) That compound – PCR 3935 – proved active in tests of antiplatelet aggregation activity (Maffrand Tr. 1638), and, after attempts to prepare it as both hydrochloride and bisulfate salts had failed, Sanofi prepared it as a hydrobromide salt. (Maffrand Tr. 1640.) Concerned, however, that PCR 3935 might be converted in the human body into carboxylic acid – which could render the compound therapeutically inactive – Sanofi synthesized a new compound in July 1980 by replacing the ethyl ester substituent of PCR 3935 with a methyl ester ($O=C-O-CH_3$) substituent. (Maffrand Tr. 1638-40.) Sanofi designated that compound – a racemic mixture prepared as a hydrochloride salt – as PCR 4099. (Maffrand Tr. 1640-41.) The non-salt (free base) form of PCR 4099 is described by the chemical formula methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o-chlorophenyl-acetate, or "MATTPCA." The nomenclature "methyl α-(4,5,6,7-tetrahydro-thieno(3,2-c)-5-pyridyl)-o-chlorophenyl-acetate" is

equivalent to "methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate." (Fact Stmt. at ¶ 31.)

Testing showed that PCR 4099 exhibited more antiplatelet activity and was better tolerated than ticlopidine. (Maffrand Tr. 1641.) Nonetheless, Sanofi continued to synthesize and test other racemic carboxylic acid and ester derivatives of ticlopidine, as well as derivatives with amide ($O=C-NR_2$) substituents. (Maffrand Tr. 1641-43.) In total, Sanofi synthesized approximately 70 carboxylic acid, ester, and amide derivatives of ticlopidine, all of which were racemic mixtures. (Maffrand Tr. 1636-1637; 1642.) Many of these compounds were subjected to a battery of tests of pharmacological activity, including four tests known as the bleeding-time test, the silk-thread test, the collagen test, and the ADP test.[3] (Maffrand Tr. 1641; Hanson Tr. 2226, 2232-33, 2238-39, 2243, 2246-67.) These were screening tests "designed to quickly screen a large number of candidate compounds in order to identify a manageable number of compounds [for] more sophisticated testing." (Hanson Tr. 2226-27; *see also* Maffrand Tr. 1644, 1646.) Sanofi's expert Dr. Stephen R. Hanson gave testimony at trial – which the Court credits – that conclusions drawn from such tests are "tentative" and that "it would be risky to extrapolate the results of these tests" – performed only in rats – to other animals or humans. (Hanson Tr. 2227.)

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[3] ADP refers to adenosine diphosphate.

III. *The '596 Patent and Its Non-U.S. Counterparts*

In July 1982 and July 1983, Sanofi applied for French and U.S. patents, respectively, on the class of thienopyridines having carboxylic acid, amide, and ester substituents. An internal Sanofi memorandum authored by Dr. Maffrand and dated February 11, 1982 stated that the patent would cover "PCR 4099 and its analogues." (Defendant's Exhibit ("Def. Ex.") 632.) The memorandum also noted that based on pharmacological testing, "[t]he most interesting esters were: PCR 4099, 4316, SR 24593, [and] SR 24597" and "[t]he most interesting amides were: PCR 4317, 4535, [and] 4516." (*Id.*) The application that was filed in the United States matured into the '596 patent, which issued on July 16, 1985 and listed Maffrand, Aubert, and Ferrand, among others, as inventors. The '596 patent is entitled "Thieno [3,2-c] Pyridine Derivatives and Their Therapeutic Application," and describes a genus of compounds that exhibit blood-platelet aggregation inhibition and anti-thrombotic activity. (Fact Stmt. at ¶ 27; '596 patent at col. 8, ll. 26-39.)

Sanofi also obtained European patent EP099802 ("the '802 patent") and Canadian Patent No. 1,194,875 ("the '875 patent") over the same class of compounds. These patents were also published more than a year before February 17, 1987, the foreign priority filing date of the '265 patent.

A. *The Specification of the '596 Patent*

The general formula described in column 1 of the '596 patent specification – which has two variables (X and Y) – depicts a racemate in non-salt (free base) form. The general formula covers an extremely large

number of compounds covered by providing for various substituents in place of the X and Y groups. (McClelland PI Tr. 494; Davies Tr. 1913-14). Each of the X and Y variables can be one of a number of enumerated substituents, with thirty-seven possibilities for the X variable and 1710 possible choices for Y. Multiplying these variables by the number of pharmaceutically acceptable acid addition salts yields an even higher number. Dr. Maffrand testified at trial that the patent covers "millions of compounds if we take into account all the combinations possible of products and salts." (Maffrand Tr. 1771.) Similarly, Sanofi's expert Dr. Davies testified that the patent covers "several millions of compounds." (Davies Tr. 1914.)

The general formula does not describe any individual enantiomer and does not describe how to obtain the enantiomers of any racemate; as drawn, the general formula describes a racemic mixture only. (Davies Tr. 1913.) However, the specification states that with respect to the general formula, "[t]he invention relates both to each enantiomer and their mixture." ('596 patent at col. 1, ll. 40-41.) The specification also sets forth that the thienopyridine compounds within the genus covered by Claim 1 can be made into addition salts with pharmaceutically acceptable mineral or organic acids or a mineral base. ('596 patent at col. 1, ll. 42-51.)

In addition, the '596 patent specification gives twenty-one examples of compounds included within the genus compound "to exemplify and to illustrate the different substituents which were claimed in the general formula." (Maffrand, PI Tr. 138; '596 patent at cols. 3-8.) These different compounds are de-

scribed in the patent as different salts forms – including hydrobromide, hydrochloride, and bisulfate salts. (Maffrand, PI Tr. at 139-140.) Specifically, three of the examples are shown as hydrochloride salts and four of the examples are shown as bisulfate salts. (Snyder Tr. 236.) The first of the twenty-one examples in the '596 patent – Example 1 – is PCR 4099, prepared as a hydrochloride salt. (Maffrand, PI Tr. at 139.) Neither Example 1, nor any other example set forth in the specification, refers to the individual or separated enantiomers of PCR 4099 or, for that matter, of any other exemplified compound. Furthermore, there is no example in the '596 patent of a methyl ester – such as PCR 4099 – prepared as a bisulfate salt. (Banker Tr. 1328.) In addition, the pharmaceutical formulations provided as non-limiting examples at the end of the specification do not show a bisulfate salt in the solid dosage form. (McClelland Tr. 1178-79; '596 patent at col. 12, ll. 3-28.)

The specification of the '596 patent also describes the compounds covered by the patent as exhibiting "an excellent tolerance and a low toxicity." ('596 patent at col. 8, ll. 42-43.) In the 1980s, Sanofi scientists commonly used the terms "tolerance" and "tolerated" to denote a compound's relative toxicity and described compounds that performed well in sub-acute and acute toxicity tests as "not very toxic" or "better."[4] Dr. Maffrand testified that he considers "toxic-

[4] The practice of referring to "tolerance" in the context of acute toxicity testing is not unique to Sanofi. Patents of companies other than Sanofi use the term "well-tolerated" to refer to results obtained through acute toxicity testing. *See, e.g.*, U.S. Patent No. 4,242,360 (Dec. 30, 1980) at col. 3, ll. 12-23 (basing

ity" to be "included in tolerance." (Maffrand Tr. 1664.) Dr. Frédéric Lacheretz, the deputy head of Sanofi's toxicology department in the mid-1980s, testified that the terms " 'more toxic than' [or] 'less well-tolerated than' . . . mean the same thing." (Lacheretz Tr. 2392.) In addition, Dr. Hanson testified that the terms toxicity and tolerance are "not necessarily mutually exclusive." (Hanson Tr. 2224.) Similarly, Apotex's expert, Dr. Gilbert Banker, agreed that "not toxic" means that a substance "won't make you sick, won't affect your physiologic functions, won't deleteriously affect your organs or even produce untoward side effects," and that non-toxic has the same meaning as "well tolerated." (Banker Tr. 1294.)

The Court credits Dr. Hanson's testimony that "[u]nless you're talking about a formally-described toxicology or tolerance study, the term tolerance . . . is commonly used as a general term that can describe toxic side effects as well as less severe side effects." (Hanson Tr. 2225-26.) Furthermore, the Court finds that the use of the terms "well-tolerated" and "less well-tolerated" is not restricted to descriptions of a drug's performance in tests at therapeutic doses only. (Graham Tr. 2424.) Apotex has failed to persuade the Court that those terms cannot appropriately be used to describe performance in tests at supra-therapeutic doses, including subacute and acute toxicity tests. (*See* Graham Tr. 2424; Hanson Tr. 2224; Lacheretz Tr. 2359; Rodricks Tr. 2495.)

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an assessment of tolerance on the results of acute toxicity testing) (Pl. Ex. 447); *see also* Snyder Tr. 714-17.

B. *The Claims of the '596 Patent*

As described above, Claim 1 sets forth a general formula that covers millions of compounds, including "their addition salts with pharmaceutically acceptable mineral or organic acids . . . including both enantiomeric forms or their mixture." ('596 patent at col. 12, ll. 30-68, col. 13, ll. 1-19.) Claim 8 covers the same genus of compounds as Claim 1, but claims their "therapeutic compositions." Claim 8 reads:

> A therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing an effective amount of a compound of claim 1, or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid with mineral bases, or one of the two enantiomers or their mixture and a pharmaceutically acceptable carrier.

('596 patent at col. 14, ll. 5-11.)

Claims 2 through 7 correspond to particular racemates, and Claim 2 specifically claims MATTPCA, or the free base of PCR 4099:

> Methyl α-(4,5,6,7-tetrahydro-thieno(3,2,c)-5-pyridyl)-o.chlorophenyl-acetate.

('596 patent at col. 13, ll. 19-20.)

Claims 2 through 7 do not include the language "both enantiomeric forms or their mixture' or "their addition salts." Claim 2, therefore, does not expressly claim any salt form of MATTPCA. (Davies Tr. 1917-19; Byrn Tr. 2134.) In addition, Claim 2 does not include a stereochemical descriptor (e.g., "*d*-" or "*l*-")

that identifies it as referring to an individual enantiomer.

C. *Tests of Pharmacological Activity Reported in the '596 Patent*

As noted above, prior to Sanofi's application for the '596 patent, several racemic compounds covered by the general formula of Claim 1 were tested for platelet aggregation inhibition activity. Results of those tests – the bleeding-time test, the silk-thread test, the collagen test, and the ADP test – were reported in the specification to the '596 patent. (Hanson Tr. 2226, 2232-33, 2243, 2246.)

Table I reports the results of the ADP test in which nine compounds, including PCR 4099 – which is listed as Derivative 1, were tested; most of the compounds demonstrated significant activity. At the doses at which they were tested, Derivative 4 demonstrated activity that was not meaningfully different from that of PCR 4099. (Snyder Tr. 633-35; '596 patent at col. 9, ll. 31-55.) In the collagen test reported in Table II, twelve compounds were tested, and, again, most of the tested compounds demonstrated significant activity. At the doses that were tested, Derivatives 9, 4, and 10 demonstrated activity quantitatively superior to that of PCR 4099, although Sanofi's expert Dr. Hanson described the activity levels of those compounds as comparable to that of PCR 4099. (Hanson Tr. 2244-46; '596 patent at col. 10, ll. 1-31.) In the bleeding-time test, reported in Table III, six compounds were tested. All the tested compounds, including PCR 4099, demonstrated maximal inhibition of blood clotting activity. (Snyder Tr. 641; Hanson Tr. 2232-33, 2237-38; '596

patent at col. 10, l. 55, col. 11, l. 5.) In the silk-thread test reported in Table IV, most of the six tested compounds demonstrated significant activity. At the doses that were tested, two of the six compounds, Derivative 3 and Derivative 10, demonstrated activity quantitatively superior to that of PCR 4099. (Snyder Tr. 641-42; '596 patent at col. 11, ll. 35-51.) Again, Sanofi's expert Dr. Hanson testified, however, that "[f]or compounds No. 3, 10, [PCR] 4099, and No. 2, all of which did very well, it is not possible to further rank their effects." (Hanson Tr. 2241.)

As noted above, Dr. Hanson testified that the pharmacological activity data presented in Tables I-IV of the '596 patent is not an appropriate scientific basis on which to rank the relative performance of the compounds – except in cases where a high dose produces little or no activity. (Hanson Tr. 2226-27, 2241, 2246.) These were screening tests used to make rough determinations of activity versus inactivity. In addition, because the screening tests were performed in rats, inferences as to how the tested compounds would perform if administered to humans would be tentative because many drugs behave differently in rats and human beings. As a result, it "would be risky to extrapolate the results of these tests" to any other animal or to human beings. (Hanson Tr. 2227-29.)

Furthermore, the tests did not provide enough data points to construct a dose-response curve for each compound; a dose-response curve is a tool used to compare the relative potency of different compounds. (Hanson Tr. 2235.) The lack of data points made it impossible to derive an "ED_{50}" value, the dose at which each compound produces half its

maximal response, which is a similar tool of comparison. (Snyder Tr. 630-32; Maffrand Tr. 1646; Hanson Tr. 2236-37.) Finally, nearly all of the compounds were tested at only one or two dose levels (Snyder Tr. 642-43), making it impossible to draw conclusions about how the compounds would perform at lower doses. (Hanson Tr. 2238.) For these reasons, the Court finds that a person of ordinary skill in the art would not discern a preference for PCR 4099 based on the pharmacological testing data in the '596 patent. (Hanson Tr. 2250.)

D. *The Canadian '875 Patent*

As noted above, the '875 patent is the Canadian counterpart to the '596 patent. (Def. Exs. 206; 1235.) Claim 1 describes a "procedure for preparing derivatives of general formula (I)"-the same general formula claimed in Claim 1 of the '596 patent. With regard to the general formula, the '875 patent also claims "the two enantiomers or their mixture." In addition, after describing the procedure for preparing certain compounds, the claim states that "then the corresponding derivative sought is obtained, which is isolated and, if desired, its enantiomers separated and/or it is salified by mineral or organic acid action." (Def. Ex. 1235.)

E. *The European '802 Patent*

U.S. Patent No. 5,989,578 ("the '578 patent") – a patent held by Sanofi which issued in 1999 – states that clopidogrel is "described" in EP 099 802, the European counterpart to the '596 patent. Two factors militate against giving that statement any credence. First, the application for the European '802 patent was filed in July 1983, well before Sanofi's separa-

tion of PCR 4099 into its enantiomers or the formulation of the dextrorotatory enantiomer of PCR 4099 – clopidogrel – as a bisulfate salt, as described below. (Maffrand Tr. 1672-73.) Second, a named inventor of the '578 patent – Dr. Pierre Savi – testified that the statement in that patent that clopidogrel is described by the European '802 patent is "incorrect," and that he had not personally read the European patent until his deposition relating to this action. (Savi 8/21/03 Dep. 164-65, 314-17.) Dr. Savi also testified that other named inventors listed on the '578 patent are biologists, not chemists. (*Id.* at 317.) Accordingly, the Court does not credit the alleged disclosure in the '578 patent and does credit Dr. Savi's unequivocal later statement that clopidogrel is not described by the '802 patent.

IV. *The Development of PCR 4099 and Its Enantiomers*

Sanofi's decision to further develop PCR 4099 required clinical testing, which in turn required Sanofi to synthesize large quantities of the drug in tablet form. From 1980 until 1987, PCR 4099 was the subject of more than fifty different types of tests in animals and humans, and Sanofi spent "tens of millions of dollars" on those tests. (Maffrand PI Tr. 144.) Sanofi also performed additional pharmacological and toxicological studies, as well as metabolic and pharmacokinetic studies. (Maffrand PI Tr. 143.) Between 1983 and 1987, Sanofi conducted acute and long-term chronic toxicity tests on PCR 4099 in rats, mice, and baboons. In each test and in each species, convulsions were observed at certain dose ranges. (Lecheretz Tr. 2362-70; Rodricks Tr. 2481-83.) A one-year chronic toxicity study in baboons in 1987

showed convulsions at all doses, including the lowest dose tested, 25 mg/kg, and demonstrated that more convulsions were observed at higher doses. (Rodricks Tr. 2481-82.)

During 1985, Sanofi representatives, including Dr. Maffrand, made poster presentations and distributed corresponding abstracts concerning their work on thienopyridines – and, in particular, PCR 4099 – at conferences of the International Society for Thrombosis and Hemostasis held in San Diego and Jerusalem. (Maffrand Tr. 1680; *see also* Def. Exs. 183, 184, 185, 186, 188, 224, 308, 418, 427.) The abstract prepared for the San Diego conference regarding PCR 4099 stated that the compound "exhibits the same broad spectrum of antiaggregating effect as ticlopidine in animals but is 40 times more potent in rats and 10 times in baboons." (Def. Ex. 184.) According to Sanofi's expert Dr. Hanson, the abstracts prepared for both conferences informed a person of ordinary skill in the art that "PCR 4099 exhibits activity in both humans and animals against platelet aggregation, and specifically the activity seems to be specially active toward the ADP pathway of platelet aggregation." (Hanson Tr. 2219-20.) Dr. Maffrand testified that Sanofi's "main goal was to inform the scientific community of the potent antiplatelet and antithrombotic activities of PCR 4099" and "to show that the compound was much more effective than ticlopidine." (Maffrand Tr. 1680.)

PCR 4099 was the only compound covered by the '596 patent that was publicized at the San Diego and Jerusalem conferences. (Maffrand Tr. 1736, 1748-49.) The posters and abstracts did not, however, discuss in any way the stereoselectivity of platelet inhibition

by the enantiomers of PCR 4099 or, for that matter, make any reference at all to the enantiomers of PCR 4099. (Maffrand Tr. 1681-86; Hanson Tr. 2220.) Accordingly, a person of ordinary skill in the art would not have drawn any inference from those materials concerning the stereoselectivity of platelet inhibition by the enantiomers of PCR 4099. (Maffrand Tr. 1681-86; Hanson Tr. 2220.) To the contrary, based on the posters and abstracts, a person of ordinary skill in the art would have concluded that PCR 4099 was under development as a promising racemic drug with several positive qualities and no significant reported negative qualities. (Snyder Tr. 290-91.)

Dr. Maffrand, however, also was aware as of 1985 that testing had showed that PCR 4099 had potential negative side effects in humans. (Maffrand Tr. 1651.) Various studies – including acute toxicity, dose-range finding, and chronic oral toxicity studies – conducted in 1983 and 1985 had demonstrated the tendency of PCR 4099 to cause convulsions in animals at particular dose levels. (*See* Plaintiff's Exhibits ("Pl. Exs.") 114, 115, 116, 117; Rodricks Tr. 2481-82.) For example, the report of a four week oral toxicity study of PCR 4099 conducted in baboons in 1983 included the observation that "[d]eath was preceded by convulsions and was most likely not accidental." (Pl. Ex. 113.) Furthermore, as a general matter, Sanofi was aware of the possibility that drugs that appeared safe in pre-clinical and clinical development might nonetheless show rare but serious side effects after launch – as had recently been the case with ticlopidine. (Maffrand PI Tr. 144; Maffrand Tr. 1651.) With the goal of finding a compound with a

better profile than PCR 4099, Dr. Maffrand decided in November 1985 to have the enantiomers of PCR 4099 separated and tested. (Maffrand Tr. 1651.)

A. *Predicting the Biological Properties of the Enantiomers of PCR 4099*

Whether it was possible for Sanofi to predict the biological properties of the enantiomers of PCR 4099 – and whether one could predict that the properties of a single enantiomer would be superior to those of its opposite enantiomer – is hotly contested by the parties to this litigation. However, in view of the prior art and the testimony given in this action, the following facts are clear.

A person of ordinary skill in the art in the mid-1980s would have known that the enantiomers of a racemate could exhibit different biological activity – including different levels of both therapeutic activity and toxicity. (Snyder Tr. 169.) As of 1984, for example, Ariëns taught that "[o]ften, only one isomer is therapeutically active, but this does not mean that the other is really inactive. It may very well contribute to the side-effects." E.J. Ariëns, "Stereochemistry, a Basis for Sophisticated Nonsense in Pharmacokinetics and Clinical Pharmacology," *Eur. J. Clin. Pharm.* 663 (1984) (Def. Ex. 138); *see also id.* at 664. Similarly, Williams & Lee taught that:

> Basic pharmacological data on the differences in activity between enantiomers suggest that there are many other drugs for which an increase in therapeutic index might be obtained by using the appropriate enantiomer rather than the racemic drug.

Kenneth Williams & Edmund Lee, "Importance of Drug Enantiomers in Clinical Pharmacology," *Drugs* 333, 348 (1985) (Def. Ex. 164); *see also* Goldstein, et al., *Principles of Drug Action (2d Ed.)* 754 (1974) (Def. Ex. 1305).

Dr. Maffrand testified at the preliminary injunction hearing that literature in the late 1970s taught that the therapeutic properties of stereoisomers could "show no obvious difference" or "could have different affinity and different activity for their known receptor." (Maffrand PI Tr. 170-71.) Where there is variation, the extent of that variation is not predictable and can be weak, moderate, or strong – a view confirmed by experts from both parties and credited by this Court. (Harden Tr. 2295-96.) Dr. Robert Snyder, an expert for Apotex, testified that without separating and testing the enantiomers of a particular racemate, a person of ordinary skill in the art could not know what the degree of difference – if any – between the properties of the enantiomers of a racemic compound would be. (Snyder Tr. 556.) The prior art, in fact, suggested that "weak" stereoselectivity – i.e., a difference in activity of ten-fold or less between two stereoisomers – was fairly common and that strong stereoselectivity – i.e., a difference in activity of 100-fold or more between stereoisomers – was less prevalent. (Harden Tr. 2295-99; Hanson Tr. 2215-16; Snyder Tr. 557-58.) In particular, the following prior art reference from Lehmann is relevant:

> When the biological activities of stereoisomers (enantiomeric and diastereomeric . . .) are compared, it is sometimes found that only one member of each pair is very active, rarely that

> both members are equally active. Very frequently though, both members exhibit the same type of activity but to a different degree. Several thousand such cases have been recorded . . . . The differences in activity for the members of any one pair . . . vary enormously, viz. from ca. 1 up to nearly 10^6.

P.A. Lehmann, et al., "Stereoselectivity and Affinity in Molecular Pharmacology," *Prog. Drug. Res.* 101, 104 (1976) (Def. Ex. 268).

The Court finds, furthermore, that a person of ordinary skill in the art would have known that absolute stereoselectivity – meaning the presence of a particular kind of activity exclusively in one stereoisomer and its total absence in the other – was uncommon. (Harden Tr. 2299-2300; Lehmann (1976) at 122.) It was also rare, moreover, if both enantiomers exhibited precisely the same levels of activity. (Snyder Tr. 172, 556-58; Lehmann (1976) at 104.) Experts from both parties agreed that even today, no scientific principles afford a basis for predicting to what degree, if any, a pair of stereoisomers will exhibit different levels of therapeutic activity and different levels of toxicity. (Snyder Tr. 563-65; Davies Tr. 2018-19; Hanson Tr. 2214.) As Dr. Davies testified, "Anything is possible . . . . You can't predict anything unless you do the experiments." (Davies Tr. 2019.) The prior art confirms this testimony as least as it relates to the separation of enantiomers as of the mid-1980s. *See* Lehmann (Def. Ex. 268) at 104 ("In spite of extended efforts . . . it has so far not been possible to explain these ratios; every biological system, sometimes every individual pair, seems to constitute a *casus sui*

generis."); W. Soudjin, "Advantages and Disadvantages in the Application of Bioactive Racemates or Specific Isomers as Drugs," *in Stereochemistry and Biological Activity of Drugs* 87, 100 (1983) (Def. Ex. 495) (noting the need for "extensive pharmacological, toxicological and clinical pharmacological research" to determine "whether it is advantageous to use racemates or enantiomers in clinical practice").

There are numerous drugs marketed as racemates in which there is no clear difference between the activities of stereoisomers, or where even though one enantiomer shows a greater level of activity, the drug is nonetheless marketed as a racemate. Dr. Thomas K. Harden, an expert for Sanofi, described fluoxetine, gatifloxacin, amphetamine, and sotalol as drugs in the latter category. (Harden Tr. 2306, 2310-15.) At the time that Sanofi decided to investigate the enantiomers of PCR 4099, Dr. Maffrand was aware that in some cases, the stereoisomers of a drug have greatly different activities (e.g., ibuprofen, thalidomide), but their metabolism *in vivo* – as opposed to *in vitro* – leads to racemization or interconversion to a different enantiomeric or achiral compound. (Maffrand PI Tr. 171-72.) Racemization is a process whereby a compound consisting of a single enantiomer is converted to a one-to-one mixture of that enantiomer and its opposite (i.e., the racemate) by the cleavage and reformation of a chemical bond at the chiral center of the molecule. (Davies Tr. 1956.) The Court finds that a person of ordinary skill in the art would also have been aware of these cases, and would have known that the risk of racemization in the body potentially eliminates any pharmacologi-

cal advantage derived from preparing the individual enantiomers. (Maffrand Tr. 1656-57.)

In addition, Sanofi's work on thienopyridines heightened Dr. Maffrand's uncertainty regarding the pharmacological potential of PCR 4099's enantiomers. Dr. Maffrand knew, for example, that thienopyridines were active only after administration to live animals, but were not active after *in vitro* exposure to isolated platelets. (Maffrand Tr. 1684-85; Harden Tr. 2325-26.) On that basis, Dr. Maffrand and his colleagues inferred that PCR 4099 required metabolic conversion – which takes place *in vivo* – to an active metabolite. (Maffrand Tr. 1684-85; Harden Tr. 2325-26; Snyder Tr. 586.) That active metabolite might not be chiral, and, even if chiral, its mechanism might not show stereoselectivity. (Maffrand Tr. 1685-86; Hanson Tr. 2213-14; Harden Tr. 2325-26; Snyder Tr. 585-86.) If so, this would mean that pursuing the enantiomers of PCR 4099 might have no benefit. This, in turn, would suggest that development efforts focus on the racemate instead of the enantiomers.

Furthermore, Sanofi's prior work on the enantiomers of racemic thienopyridine compounds did not suggest that the separated enantiomers would exhibit different types or levels of activity. (Maffrand Tr. 1696-1700). Although Sanofi had previously observed that only one of the enantiomers of PCR 1033 exhibited antiplatelet activity, the enantiomers of PCR 3549, by contrast, had exhibited equivalent levels of activity. (Maffrand 1598-99, 1604-05.) Furthermore, the Court credits Dr. Davies' testimony that a medicinal chemist would not expect PCR 1033 and PCR 4099 to behave in the same manner in the

body on the basis of any structural similarity; PCR 4099 has an ester group, which allows for significant hydrogen bonding, whereas PCR 1033 does not. (Davies Tr. 2009-14.) In sum – as experts from both parties agree – it was not possible to predict whether either enantiomer would be more or less therapeutically active – and more or less toxic – than the other. (Snyder Tr. 591-92; Davies Tr. 2014-16; McClelland PI Tr. 505-06.)

B. *Predicting Whether the Enantiomers of PCR 4099 Could Be Prepared*

In addition, Dr. Maffrand and his colleagues could not predict with any reasonable degree of certainty that they would be able to obtain the enantiomers of PCR 4099. Up until the decision to attempt the resolution of PCR 4099, Sanofi had only twice attempted – albeit successfully – to obtain the enantiomers of racemic thienopyridines, even though Sanofi had synthesized approximately 1500 thienopyridines, of which roughly 600 were racemates with chiral carbon atoms. (Maffrand Tr. 1618-19.) As of 1987, there were at least ten different methods by which a chemist could try to obtain the individual enantiomers of a chiral compound. (Davies Tr. 1921-22.) After choosing a particular technique, a chemist would also have to make numerous decisions: the choice of solvents, of reagents, of concentrations, of temperature, and of time. (Davies Tr. 1939-43.) Sanofi's expert Dr. Davies testified on direct examination that there is no way to predict which method or methods will succeed if no prior art deals with the compound at hand; practitioners will begin with a method with which they are familiar or a method for

which the necessary reagents are readily available.[5] (Davies Tr. 1939.)

As noted above, Sanofi had used diastereomeric salt formation to separate the enantiomers of PCR 1033, but had failed when trying to use that method to separate the enantiomers of PCR 3549. As of 1987, the prior art – including standard textbooks of organic chemistry – was replete with discussions of how to resolve enantiomers by diastereomeric salt formation, which was first identified by Louis Pasteur in 1853 and is sometimes referred to as "the classical method." (Davies Tr. 1925; Snyder Tr. 149-51, 155-56). The Feiser, Karrer, and Jacques references make clear that diastereomeric salt formation was a method of enantiomeric resolution that was well known in the art at the time that Sanofi chemists faced the task of obtaining the enantiomers of PCR 4099. *See* Louis F. Feiser & Mary Feiser, *Advanced Organic Chemistry* 85-89 (1961) (Def. Ex. 1322); Paul Karrer, *Organic Chemistry* 98-99 (1946) (Def. Ex. 162); Jean Jacques, et al., *Enantiomers, Racemates, and Resolutions*, 378-88 (1981) (Def. Ex. 492).

However, Dr. Davies explained that although that method is "one of the oldest methods," that does not mean that it is the best method, the easiest method to apply, or "the first one you should try." (Davies Tr. 1925-26.) As a general matter, obtaining the first crystals of any new compound through separation of diastereomeric salts is difficult. Jacques, for exam-

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[5] On cross-examination Davies did concede that at least five of the methods available would have been identified as inappropriate in the case of PCR 4099. (Davies Tr. 2023-24.)

ple, teaches that "[n]o infallible recipe exists for overcoming the resistance of a diastereomer to crystallize for the first time." (Jacques (Def. Ex. 492) at 386.) The Eliel reference confirms this point:

> Unfortunately, resolution is, in this respect, still very much a matter of trial and error, and even in the papers of experienced investigators one is apt to find, from time to time, a statement that a certain compound resisted resolution by any one of a large number of combinations of resolving agents and solvents that were tried.

Ernest L. Eliel, *Stereochemistry of Carbon Compounds* 50 (1962) (Def. Ex. 1930). *See also* McClelland Tr. 1117-21; Davies Tr. 1945-48. Although screening techniques would have allowed a person of ordinary skill in the art to improve the odds of a successful separation, diastereomeric salt separation was – and remains even today – a "paradigm of trial and error." Ton Vries, et al., "The Family Approach to the Resolution Of Racemates," *J. Angewandte Chemie* 2349 (1998) (Pl. Ex. 852); *see also* Jacques, Def. Ex. 492 at 380; McClelland Tr. 1137-39. Experts from both parties agreed that although a chemist can search the prior art for useful examples of prior resolutions of similar compounds, the precedents afford absolutely no assurance that the same configuration will succeed with a different compound. (McClelland Tr. 1118; Davies Tr. 1975; *see also* Eliel (Def. Ex. 1930) at 50.) Furthermore, the literature tends not to report failed resolution attempts. (McClelland Tr. 1135.) In the particular case of PCR 4099, the prior art offered no examples of the resolutions of chiral thienopyridines, and Apotex's

expert Dr. McClelland – in preparing for his testimony – did not find *any* reference that contained the set of conditions that Sanofi ultimately used to obtain the enantiomers of PCR 4099. (McClelland Tr. 1071.) In fact, Dr. McClelland did not find any relevant instances of the resolution of thienopyridines in the prior art. (McClelland Tr. 1127; 1230-32.)

In addition, a person of ordinary skill in the art would have recognized the possibility that it would be more difficult to prepare the enantiomers of PCR 4099 than it had been to prepare the enantiomers of PCR 1033 and PCR 3549. First, the meythl ester group attached to the chiral center in PCR 4099 made that molecule more susceptible than PCR 3549 to racemization. (Hendrickson Tr. 1498; Maffrand Tr. 1656, 1700; Badorc Tr. 1832-33.) Indeed, a person of ordinary skill in the art would have known that phenylglycine and its derivatives – of which PCR 4099 is one – are susceptible to racemization. (Badorc Tr. 1832; Davies Tr. 1956-60.) Second, because of the presence of the ester substituent on PCR 4099, the hydrogen atom located on the chiral carbon could easily be removed through the action of a base or an acid (which would be required in the course of resolution of the enantiomers). A free hydrogen in solution could then reform a bond to the same carbon atom, but it would bond on either side of that atom with equal likelihood, thereby yielding a racemate. (Davies Tr. 1958-61; 2002-04.) Third, the enantiomers of PCR 4099 would be susceptible to racemization in the acidic environment of the stomach by the same mechanism. (Davies Tr. 2004; Hendrickson Tr. 1463.)

Accordingly, neither the chemists at Sanofi nor a person of ordinary skill in the art could have reasonably expected that the separate enantiomers of PCR 4099 could be obtained at the time that Sanofi was contemplating whether to investigate them and, if obtained, they could not have predicted by what method and configuration.

C. *Resolution of the Enantiomers of PCR 4099*

In November 1985, Alain Badorc and Dr. Daniel Fréhel were asked to attempt to obtain the enantiomers of PCR 4099 in order to test whether either enantiomer would make a better drug than the racemate. (Maffrand Tr. 1650-51.) As the outset, Badorc and Dr. Fréhel decided not to attempt resolution through the formation of diastereomeric salts. The Court credits Badorc's testimony that that decision was influenced by the fact that PCR 4099 was "only barely basic and, therefore, only barely capable of carrying out a separation using diastereomeric salts." (Badorc Tr. 1829.) In addition, Badorc believed that there were few commercially available acids that were likely to form diastereomeric salts in sufficient quantities to permit resolution. (Badorc Tr. 1830.) Instead of attempting diastereomeric salt separation, Badorc decided to attempt chemical asymmetric synthesis, the method that he had successfully used to prepare the enantiomers of PCR 3549. This choice was facilitated by the commercial availability of the required starting materials. (Badorc Tr. 1829-31.)

Badorc's lab notebook and a June 12, 1986 report show that Badorc reacted the starting materials to form the enantiomers of an intermediate compound –

referred to as "OCBATH." (Pl. Ex. 50.) He then used the same "reaction sequence" that he had used in the synthesis of the enantiomers of PCR 3549. (Hendrickson 1497-98; Badorc 1836-37; Pl. Ex. 50 at S 03977-78; Pl. Ex. 51 at S 58990-91.) With PCR 4099, however, the sequence failed because the second reaction in the sequence, a condensation, yielded a racemic form of the desired product, not a pure enantiomer. (Badorc Tr. 1836-37; Pl. Ex. 50 at S 03978; Pl. Ex. 51 at S 58991.)

Badorc then tried a different approach. Starting from the racemic OCBATH, he attempted to separate that intermediate's enantiomers through the formation of diastereomeric salts with tartaric acid in isopropanol. After several crystallizations, Badorc obtained enantiomers with the same melting point and equivalent levels of optical rotation. (Badorc Tr. 1837-38; Pl. Ex. 50 at S 0379-80; Pl. Ex. 51 at S 58992-93.) Badorc then attempted to convert the enantiomers of OCBATH into those of PCR 4099 using the same cyclization reaction conditions used to prepare the enantiomers of PCR 3549. That product, however, also racemized. (Badorc Tr. 1838; Pl. Ex. 50 at S 03980; Pl. Ex. 51 at S 58993.)

Badorc also tried using diastereomeric salts to resolve the enantiomers of the acid precursor of PCR 4099, a compound designated as PCR 3068. To that end, he attempted resolution with several different chiral bases, but those efforts failed because no crystals formed. (Badorc Tr. 1839-42; Pl. Ex. 50 at S 03891.) When Badorc attempted to form diastereomeric salts of PCR 3068 with chirally pure d-camphorsulfonic acid in ethanol, crystals did form, but that effort failed because the crystals contained

salts of both enantiomers, rather than just of one. (Badorc Tr. 1841-42.)

At that point – in January 1986 – Badorc revisited the technique that he had originally been reluctant to use and attempted to resolve the enantiomers of PCR 4099 directly by diastereomeric salt formation. (Badorc Tr. 1842.) To determine what combination of acid, solvent, and concentration would yield crystals, Badorc set up a "screening" experiment with approximately thirty test tubes containing various combinations of a chiral acid (e.g., camphorsulfonic, toluoyltartaric, dibenzoyl tartaric, mandelic, and tartaric) with PCR 4099 in various concentrations and in various solvents. (Badorc Tr. 1842-43.) Badorc obtained a solid material in only one of the test tubes – a gummy substance at the bottom of the tube containing a 1:1 ratio of camphorsulfonic acid and PCR 4099 in acetone. (Badorc Tr. 1844.) No crystals were obtained in any test tube. (Badorc Tr. 1844.)

In mid-February, Badorc began an additional screening test of several test tubes with different combinations of acid, solvent, and concentration. (Badorc Tr. 1844-45.) Badorc checked the test tubes each day for crystals, the presence of which would indicate the formation of a potentially separable diastereomeric salt. (Badorc Tr. 1846.) Approximately one month after beginning the experiment, Badorc detected crystals in only one tube – the tube that contained (+) camphorsulfonic acid and PCR 4099 in a 4:10 ratio, dissolved in acetone.[6] (Badorc Tr. 1846-

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[6] Dr. Robert A. McClelland, an expert for Apotex, testified that each recrystallization takes from four hours to "perhaps

47.) As noted above, that same combination using the acid and PCR 4099 in a 1:1 ratio had not yielded crystals. (Badorc Tr. 1843-44.)

Because the small test tube reaction had not yielded a sufficient quantity of crystals for further testing, Badorc carried out a larger version of the experiment on March 18, 1986. (Badorc Tr. 1847-48; Pl. Ex. 72 at S 02014.) Risking the loss of the crystals that he had obtained, Badorc used those crystals to seed the larger version, which – after several trials – yielded a significant quantity of crystals of the levorotatory enantiomer of PCR 4099 in the camphorsulfanate form. (Badorc Tr. 1848-49; Pl. Ex. 72 at S 02014.) Using the same conditions – but substituting chirally pure 10-camphorsulfonic acid of opposite rotation – Badorc also resolved the dextrorotatory enantiomer (i.e., clopidogrel). (Badorc Tr. 1850-51; Pl. Ex. 50 at S 03986; Pl. Ex. 74 at S 02019.) Finally, to form the free base of both resolved enantiomers, Badorc reacted the camphorsulfonate salt forms with sodium bicarbonate, a base. (Badorc Tr. 1852.) Badorc verified the optical purity of the free base compounds to confirm that he had resolved the enantiomers and that they had not racemized at any stage. (Badorc Tr. 1852-53.) Nothing in the prior art – and nothing in his own experience with PCR 1033

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overnight," and that a person of ordinary skill in the art would generally wait only that long, or "maybe for a few days," to see if crystals will form. (McClelland Tr. 880, 1131.) However, in the case of Badorc's second test tube screening experiment, it took approximately *one month* for crystals to form. (Badorc Tr. 1846.) The disparity between Dr. McClelland's testimony and the factual record undermines the proposition advanced by Apotex that the resolution of the enantiomers of PCR 4099 was a simple, routine procedure.

and PCR 3549 – directed Badorc to employ the precise configuration of acid, solvent, and concentration that was ultimately successful with PCR 4099.

D. *Preparation of Clopidogrel as a Pharmaceutically Acceptable Salt*

To permit the testing and comparison of the properties of the enantiomers of PCR 4099 to those of the racemate, which had only been tested as a hydrochloride salt, Badorc prepared the hydrochloride salts of each enantiomer. (Badorc Tr. 1852-53.) As described below, pharmacological and toxicological testing showed that clopidogrel hydrochloride exhibited more antiplatelet activity than PCR 4099 and was better tolerated than the l-enantiomer, but – as a hydrochloride salt – the compound was hygroscopic (i.e., it had a tendency to absorb water from the atmosphere) and lacked stability. (Badorc Tr. 1853; Banker Tr. 1338; Pl. Ex. 48 at S 03781.) This made it a poor candidate for commercial tablet manufacture. For that reason, during May and June of 1987, Badorc searched for a salt form of clopidogrel that would be more suitable for use in commercial tablets. (Badorc Tr. 1854.)

Salts are formed by mixing an acid with a base. (Banker 1274, 1299-1300.) A basic rule of salt formation is that a weak base – such as PCR 4099 – generally requires a strong acid to form a salt.[7] (Banker 1274, 1300.) A measure of the strength of an

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[7] In addition to selecting the acid, the chemist must also choose a solvent and co-solvent in which to attempt to precipitate the crystals, and must also consider temperature and cooling rates. (Byrn Tr. 2127-29.)

acid or a base is its "pKa": a low pKa signifies a strong acid and a high pKa signifies a weak acid. (Banker 1274; Byrn Tr. 2111-12.) In 1977 and 1986, the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds and twenty-one bases as candidates for forming salts with acidic compounds. On this point, the Court credits the Berge reference and the Gould reference. *See* Stephen M. Berge, et al., "Pharmaceutical Salts," *J. Pharm. Sci.*, 1, 2-3 (1977) (Pl. Ex. 152); Philip L. Gould, "Salt Selection for Basic Dugs," 33 *Int'l J. Pharm.* 201, 202, 214-16 (1986) (Pl. Ex. 153); Byrn Tr. 2126. Of the eighty acids listed by Berge, fifty-three were used in FDA-approved drugs as of 1974; the remaining twenty-seven were commercially marketed in other countries. (Berge (Pl. Ex. 152) at 2-3; Byrn Tr. 2126.) The Berge reference also taught the pKa of each of those acids. (Berge (Pl. Ex. 152) at 2-3.)

If the difference in pKa of an acid and base is greater than two, the "delta pKa rule" is a guideline that suggests that the amount of salt present in solution – as compared to that of the unreacted acid and base – will be greater than if the difference in pKa is less than two. (Byrn Tr. 2112-15.) However, even if the pKa difference between an acid and a base is only one or zero, their reaction will still yield a 10:1 or 1:1 ratio, respectively, of protonated to unprotonated base in solution. (Davies Tr. 2064-65; Byrn Tr. 2114-16.) The presence of protonated base will, in turn, permit salt formation in solution, from which crystals of the salt might precipitate. (Davies Tr. 2064-65; Byrn Tr. 2114-16.) For that reason, a person of ordinary skill in the art would not necessarily

have excluded from consideration those acids whose pKa values differed from that of the relevant base by less than two. (Davies Tr. 2065; Byrn Tr. 2115-16.) Weak acids – where the resulting pKa difference is less than two – might even be preferable where there is the risk of acid-catalyzed racemization or hydrolysis of the base. (Byrn Tr. 2119.) Therefore, a person of ordinary skill in the art would not be able to predict from the list provided by Berge which acids would form useful salts for drug purposes. (McClelland PI Tr. 503-04.)

Depending on their properties, salts of pharmaceutical compounds can be characterized according to three general types, or "tiers." (Byrn Tr. 2109-11.) A Tier 1 salt results from the simple reaction of an acid and a base in solution, without regard to its properties. (Byrn Tr. 2109-10.) A Tier 2 salt is a solid salt that facilitates testing, but may be hygroscopic or unstable over the long term and, for either of those reasons, may not be suitable for use in tablets. (Byrn Tr. 2110.) A Tier 3 salt – the type of salt that is generally desirable for use in a drug tablet – is crystalline, non-hygroscopic, stable as a tablet, soluble in bodily fluids, dissolved fast enough to allow absorption in the body, not sticky, and without a static charge. (Byrn Tr. 2110-11, 2120-21; McClelland Tr. 1173-74.)

Formation of a crystalline salt is important for an orally administered drug such as clopidogrel, and the salt form of a drug can affect a drug's pharmacological properties because of its effect on solubility, which influences absorption in the body and bioavailability. However, the prior art teaches – and both parties' experts agreed and the Court finds –

that whether a crystalline material will form in a particular reaction of acid and base, the type of crystalline material that will form, and the properties that the crystalline material will have, are all unpredictable. (McClelland PI Tr. 503-04; McClelland Tr. 1101-02; Snyder Tr. 544-45; Byrn Tr. 2122-23.) In particular, Berge taught that:

> Choosing the appropriate salt . . . can be a very difficult task, since each salt imparts unique properties to the parent compound . . . Unfortunately, there is no reliable way of predicting the influence of a particular salt species on the behavior of the parent compound.

Berge (Pl. Ex. 152) at 1. Making reference to Berge, the Gould publication provided similar teaching nearly a decade later:

> The importance of choosing the 'correct' salt form of a drug is well outlined in a published review (Berge et al., 1977) but, although salt form can have a dramatic influence on the overall properties of a drug, the selection of the salt form that exhibits the desired combination of properties remains a difficult semi-empirical choice.

Gould (Pl. Ex. 153) at 201. In addition to this high level of general unpredictability, a person of ordinary skill in the art would have recognized that there is no correlation between a racemate and its corresponding enantiomers when it comes to making a crystalline salt. (Banker Tr. 1322-24; Davies Tr. 1955-56; Byrn Tr. 2123-25.) The physical properties of racemates and their enantiomers, as well as of

their respective salts, differ because the molecules pack differently, leading to different crystal structures. (Snyder Tr. 543-45; Banker Tr. 1321-23, 1327; Davies Tr. 1955; Byrn Tr. 2123-2125.) In other words, the salt form of a racemate may produce a very different crystalline structure than the same salt forms of the enantiomers of that racemate. For that reason, even if a person of ordinary skill in the art looking at the '596 patent had concluded that PCR 4099 should be reformulated as a bisulfate salt, that would not imply that the enantiomers of PCR 4099 – if obtained – should also be prepared as bisulfate salts. (Davies Tr. 1914-15; Byrn Tr. 2136-38.) Accordingly, there would have been no way for a person of ordinary skill in the art to deduce from the examples of the '596 patent that clopidogrel would form a bisulfate salt and that it would be a Tier 3 crystalline salt. (Davies Tr. 1915; Byrn Tr. 2136.)

Tasked with identifying a suitable crystalline, non-hydrochloride salt of a drug, a person of ordinary skill in the art would look to the approximately fifty pharmaceutically acceptable (i.e. FDA-approved) acids identified by the prior art. (McClelland PI Tr. 490-91; Byrn Tr. 2126.) This was essentially the approach taken at Sanofi, where Badorc and his colleagues reacted clopidogrel with an array of approximately twenty-one different acids – only about ten of which were strong acids – in different solvents. (Badorc Tr. 1854-55; Maffrand 1773-74; Pl. Ex. 73 at S 02245, S 02248-60, S 02276; Pl. Ex. 74 at S 02054.) Badorc used both strong and weak acids because it was not possible to predict which acid would yield a crystalline salt meeting all of the criteria for a suitable pharmaceutical tablet. (Badorc Tr. 1854-55;

Byrn Tr. 2140-46.) When Badorc attempted to create the sulfate form of clopidogrel, the reaction instead resulted in its bisulfate salt. (Badorc Tr. 1797-98.) Although sulfuric acid was one of the first acids that he tried, Badorc continued to test other acids. (Badorc Tr. 1854-55; McClelland Tr. 2565.) This was not unreasonable. On the contrary, it would have been reasonable for a person of ordinary skill in the art to try a variety of weak acids and strong acids so as not to overlook potential Tier 3 salts. (Badorc Tr. 1854-55; Davies Tr. 1969-70; Byrn Tr. 2144-46.)

The bisulfate salt proved to be the only salt with the optimal properties: a high melting point, long-term stability, non-hygroscopicity, and good solubility. (Badorc Tr. 1855; Banker Tr. 1357.) Although a person of ordinary skill in the art would have known that hydrochloric acid, hydrobromic acid, and sulfuric acid were the three strongest acids used in pharmaceutical salts, a person of ordinary skill in the art would not have reasonably expected the bisulfate salt of clopidogrel to have the highly favorable combination of properties that it turned out to possess. (Byrn Tr. 2164.) First, the highly acidic nature of the bisulfate posed a significant risk of racemization, which made it unattractive for use with an enantiomeric compound. (Byrn Tr. 2158; Davies Tr. 1970-72.) Second, the Court credits the testimony from Dr. Stephen R. Byrn, an expert for Sanofi in the area of solid state chemistry, that the relevant prior art not only provided no positive indication that sulfuric acid would lead to a successful crystalline salt, but the prior art in fact would have led a person of ordinary skill in the art away from sulfuric acid in the case of clopidogrel. (Byrn Tr. 2160-63.) Specifically, the

Gould publication taught that to avoid hygroscopicity – the problem posed by the hydrochloride salt of clopidogrel – one should avoid polar salts, which would include the bisulfate. (Gould (Pl. Ex. 153) at 210-13; Byrn Tr. 2158-59, 2162.) Instead, Gould pointed to the use of carboxylic acids, which, in the case of clopidogrel, proved unsuccessful. (Gould (Pl. Ex. 153) at 210-13; Byrn Tr. 2160-63.) Third, another prior art reference – the Berge publication – did not even list the bisulfate salt in its list of FDA-approved commercially marketed salts; the bisulfate appears only on the list of non-FDA approved salts, making it all the more surprising that the bisulfate salt of clopidogrel, in fact, proved to be a highly suitable pharmaceutical formulation. (Berge (Pl. Ex. 152) at 2-3; McClelland PI Tr. 491.) For all of these reasons, a person of ordinary skill in the art could not have reasonably expected that the bisulfate salt of clopidogrel would be the optimal pharmaceutical salt form of the compound.

V. *The Biological Properties of Clopidogrel*

A. *The Pharmacological Properties of the Enantiomers of PCR 4099*

Testing demonstrated that the dextrorotatory enantiomer – clopidogrel – exhibited good platelet inhibition activity. (Maffrand Tr. 1659.) By contrast, the levorotatory enantiomer was "completely ineffective"; it showed no statistically significant activity in any assay. (Maffrand Tr. 1659; Snyder Tr. 2526-29.) This absolute stereoselectivity of platelet inhibition for the enantiomers of PCR 4099 was unexpected in light of the prior art. (Davies Tr. 2014-

15, 2018-19; Hanson Tr. 2214, 2216, 2250-51; Harden Tr. 2338.)

A finding that the absolute stereoselectivity of the enantiomers of PCR 4099 was unexpected was not undermined by the prior art regarding ADP platelet receptors, including the work of Dr. Robert Colman, a platelet physiologist. Apotex has failed to persuade the Court that Colman's work – in particular, a 1984 article co-authored by Colman – would have made Sanofi's results unsurprising to a person of ordinary skill in the art. *See* Robert W. Colman & William R. Figures, "Characteristics of an ADP receptor mediating platelet activation," *Molecular & Cellular Biochem.* 101 (1984) (Def. Ex. 519). As of 1987, platelet physiologists suspected the existence of one or more platelet receptors for ADP, and they knew that the suspected receptors were stereoselective for the naturally occurring stereoisomer of ADP. (Hanson Tr. 2216-17; Harden Tr. 2321-22.) Based on that phenomenon, however, a person of ordinary skill in the art would not have drawn the inference that chiral antagonists would inhibit platelet activation stereoselectively. (Hanson Tr. 2217-18; Harden Tr. 2322-23.) In the early 1980s, Dr. Colman identified a protein on the surface of platelets – aggregin – that he posited was a receptor for ADP. (Colman Tr. 1015-20.) Dr. Colman's work did not, however, address whether thienopyridines inhibited platelet activation through interaction with aggregin or any other protein – his work in the 1980s did not involve thienopyridines. (Snyder Tr. 605-06; Colman Tr. 1024-25; Maffrand Tr. 1676-77.) Nor did Dr. Colman's work address whether aggregin interacted with any molecule in a stereoselective fashion; he did

not compare the effects of different stereoisomers of the same chiral molecule on aggregin or platelet activation. (Harden Tr. 2334-35; Snyder 605.) Thus while Colman's work, including the 1984 article, relates generally to the problem of platelet aggregation that Sanofi's research also addressed, the 1984 article was of no particular significance to the properties that Sanofi discovered clopidogrel to possess.

B. *The Toxicological Properties of the Enantiomers of PCR 4099*

Sanofi also subjected the enantiomers of PCR 4099 to a battery of toxicological testing. In acute toxicity testing of PCR 4099 and its enantiomers in March 1987, Sanofi calculated the doses at which each of the compounds is lethal in rats. The tests – reported internally in a research memorandum dated May 18, 1987 – showed that the LD_{50} for clopidogrel (4316 mg/kg) was much higher than the LD_{50} of either PCR 4099 (1615 mg/kg) or the l-enantiomer (1702 mg/kg).[8] (Lacheretz Tr. 2377-79; Pl. Ex. 118 at 11.) This showed that the acute toxicity of the levorotary enantiomer and PCR 4099 was "very different" – i.e., significantly higher – than that of clopidogrel. (Lacheretz Tr. 2379.) The absolute lethal doses of PCR 4099 and the levorotatory enantiomer were similar (2000 mg/kg) and were also lower than the absolute lethal dose of clopidogrel (5000 mg/kg). (Maffrand Tr. 1688-89; Pl. Ex.118 at 2.) Furthermore, convulsions were observed in animals

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[8] The LD_{50} is the calculated dose of a compound at which 50 percent of the test animals administered the compound die. Similarly, the LD_{10} indicates the single dose at which 10 percent of the animals tested die. (Lecheretz Tr. 2358.)

receiving PCR 4099 and the l-enantiomer in a comparative acute toxicity study, but no convulsions were observed in animals receiving clopidogrel, including clopidogrel in any of its hydrochloride, bisulfate, or hydrobromide forms. (Lacheretz Tr. 2377; Pl. Ex. 130.) In sum, the data collected from tests conducted by Sanofi – data which was later reported in the '265 patent – showed (1) that the levorotatory enantiomer is lethal at significantly lower doses than clopidogrel, and (2) that the levorotatory enantiomer is neurotoxic, but clopidogrel is not. (Graham Tr. 2423-24; Maffrand Tr. 1688-90; Lacheretz Tr. 2387.) According to Sanofi's toxicologist Dr. Lecheretz, Sanofi concluded from these results that clopidogrel was "much less toxic or, in other terms, much better tolerated" than both the levorotatory enantiomer and PCR 4099. (Lacheretz Tr. 2380.)

That conclusion was amply supported at trial. Dr. Joseph V. Rodricks, an expert for Sanofi, explained that a drug's therapeutic index is a measure of a drug's safety and is calculated based on the ratio of its toxic dose to the dose that "reflects efficacy," i.e., the dose that has a therapeutic effect. (Rodricks Tr. 2488.) A higher therapeutic index indicates a safer drug. (Rodricks Tr. 2488-90.) Based on data from short-term studies, Dr. Rodricks testified that clopidogrel has a much higher therapeutic index than PCR 4099, which indicates clopidogrel's safety advantage over the racemate. (Rodricks Tr. 2494-95.) Based on data derived from longer-term studies, Dr. Rodricks determined that PCR 4099's low therapeutic index demonstrates a valid safety concern. (Rodricks Tr. 2496-99.) In contrast, serious toxic

effects were not observed in response to any dose of clopidogrel in the longer-term studies. (Rodricks Tr. 2495-98.)

Based on the documentary evidence and testimony relating to both the pharmacological and toxicological properties of clopidogrel, the Court finds that the prior art offered no basis to reasonably expect that the resolution of PCR 4099 would yield an inactive enantiomer that was also less well-tolerated than the active enantiomer. (McClelland PI Tr. 505-06; Snyder Tr. 591-92; Harden Tr. 2250-51.) Accordingly – and most importantly – the fact that clopidogrel was both the more active enantiomer of PCR 4099 *and* was better tolerated than the levorotatory enantiomer would have been unexpected to a person of ordinary skill in the art prior to obtaining the separate enantiomers and testing them.

C. *Sanofi's Decision to Discontinue Development of PCR 4099*

In March 1987, Pierre Simon, then the head of research and development at Sanofi, reviewed the pharmacological and toxicological studies of PCR 4099 and its enantiomers. At that time, Dr. Maffrand was reluctant to discontinue the development of PCR 4099 in favor of clopidogrel. (Maffrand PI Tr. 154.) In an internal memorandum dated March 31, 1987, Dr. Maffrand noted that tests had shown PCR 4099 to be "consistently active in healthy volunteers," but that it had been "consistently ineffective in patients" for reasons yet unknown. (Def. Ex. 622.) Maffrand further noted that the active enantiomer of PCR 4099 showed less acute toxicity in rats and mice than the inactive enantiomer, but that there was not yet data

available on subacute toxicity. (*Id.*) Nonetheless, Dr. Maffrand expressed doubts about abandoning Sanofi's work on PCR 4099 in favor of the active enantiomer, noting that "[i]t isn't the inactive enantiomer that is causing the problems with PCR 4099 we are encountering today." (*Id.*) At the preliminary injunction hearing, Dr. Maffrand testified that by that time, Sanofi had performed more than fifty tests on PCR 4099 from 1980 to 1987, including phase I human trials, at a cost of "tens of millions of dollars." (Maffrand PI Tr. 143-44, 152-53.) To develop clopidogrel, Sanofi would not have been able to rely on the data from tests that related to PCR 4099. As a result, Dr. Maffrand at that time viewed switching to the development of the active enantiomer instead of the racemate as a four year setback. (Maffrand PI Tr. 155.)

Nonetheless, Simon decided to terminate the development of PCR 4099 in favor of focusing on clopidogrel. (Maffrand Tr. 1666.) In an April 16, 1987 internal memorandum setting forth his decision, Simon wrote the following:

> These studies have demonstrated that only the D form is active and that, moreover, the L form was more toxic and was specifically responsible for convulsions observed in animals at high doses. Under these conditions, it appears clear to me that we cannot envision development of the [racemate], and I have decided to stop this development. Our efforts therefore are turning to the D form and we are taking all possible steps to reduce lost time to a minimum.

(Pl. Ex. 57t.) Accordingly, the development of PCR 4099 was stopped.

On November 6, 1987, Sanofi held a meeting in Japan with its partners in a joint venture. That meeting included discussion of the decision to abandon PCR 4099. A memorandum describing the meeting suggests that the reason for discontinuing the development of PCR 4099 in favor of clopidogrel was based on Sanofi's discovery that the therapeutic activity was located only in the dextrorotatory enantiomer and that "the [l-enantiomer] is more toxic than the [d-enantiomer] qualitatively and quantitatively." (Def. Ex. 13.) Moreover, the memorandum also notes the following:

> The trend in regulatory requirements would have made it difficult to get the NDA approval with the racemic either in France or in Europe or in the United States. It is the reason why SANOFI stopped the development of PCR 4099. In any case, our decision was not due to problem[s] in preclinical or in clinical studies, particularly no problem of G.I. intolerance was noted in volunteers, showing an advantage over Ticlopidine. For Japan, it also seems that it would not have been possible to apply for a NDA with the racemic in such a case.

(*Id.*) Nonetheless, because the November 7, 1987 meeting took place several months after Simon's April 16, 1987 memorandum – which focused specifically on the neurotoxicity problems associated with PCR 4099 – and, more generally, well after Sanofi had decided to split the enantiomers of PCR 4099, the Court credits the extensive trial testimony and

documentary evidence that the decision to discontinue the development of PCR 4099 in favor of clopidogrel was based on the sub-optimal side effect profile of PCR 4099, not because of any specific concern raised by Sanofi's joint venture partner or any nascent regulatory trend mandating the investigation of enantiomers where a racemic drug was proposed.

VI. *The '265 Patent*

A. *The French Patent*

As described above, Sanofi applied for a French patent claiming clopidogrel and its salts on February 17, 1987 – at a time when Sanofi was still actively engaged in developing PCR 4099. Prior to filing the application, Fréhel put together an initial draft of that application, which he circulated on December 1, 1986. That draft included the following statement in the specification: "In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Exs. 8 at S 91129, 425 at S 91129.) That statement was based on observations made by Sanofi scientists in the course of pharmacological testing of the enantiomers of PCR 4099. (Maffrand Tr. 1659-64.) That statement remained in the version of the application that was submitted to the French regulator, and, eventually, to the PTO in the United States.

On December 30, 1986, after Fréhel's initial draft had been circulated internally, Michel de Haas, head of Sanofi's legal department, circulated a memo with

the heading "Patentability of the two enantiomers of PCR 4099." In that memo, Haas wrote:

> [I]f we ever develop the active isomer [i.e., clopidogrel], it would be very useful to have a patent for this isomer (prolonging our monopoly, prohibiting its use by third parties in countries where [PCR] 4099 is not patented as a product . . .). Issuing such a patent will only be effective, at least in countries with an examination process, if we make mention of an 'unexpected' advantage (whether this is the reason for developing the product or not).

(Def. Ex. 628.) Haas also noted that Sanofi would not develop the active enantiomer if it showed "no major therapeutic advantage" over PCR 4099 considering the cost of manufacture, either "by stereospecific synthesis or by separation from the racemic." (*Id.*) In the alternative, Haas noted that they might find the active enantiomer "very attractive" if, for example, "it does not have . . . some of the objectionable side effects of PCR 4099 (bleeding . . .)." (*Id.*)

In late January 1987, Jacqueline LaForest, an in-house French patent attorney at Sanofi, reviewed Fréhel's draft application for the French patent. (Maffrand Tr. 1673.) Although LaForest had studied chemical engineering as an undergraduate student, she did not have training in pharmacology or toxicology. (Maffrand Tr. 1673.) In comments dated January 26, 2007 to the draft application, LaForest wrote: "[t]he pharmacology study does not lead to surprising activity; we will not pass the examiner's hurdles without other results." (Def. Ex. 304.) Laforest also wrote: "If I understood the text [of the application]

correctly, PRP aggregation results [i.e., results of testing of the compounds' ability to inhibit platelet aggregation] are missing . . . ." (*Id.*) However, those very results in fact appeared prominently in the application that Laforest was reviewing. (Snyder Tr. 645-46; Maffrand Tr. 1674; Def. Ex. 304.) Furthermore, LaForest's written comment on the lack of "surprising activity" was made before the results of subsequent March 1987 toxicology studies were known. (Maffrand PI Tr. 152.)

B. The U.S. Patent

On February 12, 1988, Sanofi filed an application in the United States for a patent on clopidogrel and certain of its salts. The U.S. application, as had the French application, contained the statement: "In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Ex. 9 at CLO-DRL 51362.)

In support of that statement, Sanofi's application reported the results of three different pharmacological tests and one acute toxicity test. The acute toxicity test showed that clopidogrel was lethal at doses that were double those at which the levorotatory enantiomer and the racemate were lethal. (*Id.* at CLO-DRL 51379-80.) This demonstrated that clopidogrel was much less toxic than the levorotatory enantiomer. (Maffrand PI Tr. 251-53; Maffrand Tr. 1688-89; Graham Tr. 2424.) In addition, between the dates that Sanofi filed the French patent application and the U.S. patent application, Sanofi scientists had

conducted additional toxicological tests, the results of which – as described above – demonstrated that the levorotatory enantiomer and PCR 4099 caused convulsions at doses which clopidogrel did not. (Maffrand PI Tr. 151-52.)

The examiner of the application for the '265 patent was Bernard L. Dentz, the same examiner who had approved the '596 patent. On November 4, 1988, Dentz initially rejected Claims 1-5 and Claims 10-11 as unpatentable because he believed the disclosure of PCR 4099 in the '596 patent anticipated them. (Fact Stmt. ¶ 21.) In the rejection, however, Dentz stated that Sanofi could correct its application by adding the limitation "substantially pure" as a means of distinguishing the claims of the '265 patent from the claims of the '596 patent. (*Id.*) Dentz also noted that if Sanofi made that amendment, a basis for the invention's patentability was Sanofi's reported data showing that the "toxicity" of the l-enantiomer "is markedly higher" than that of the d-enantiomer. (*Id.*)

On January 9, 1989, Sanofi amended claims 1-5 by inserting the phrase "substantially separated from the levo-rotatory isomer." (*Id.* ¶ 23.) On January 30, 1989, the PTO issued a Notice of Allowability for the amended claims. (*Id.* ¶ 26.) The '265 patent issued on July 11, 1989. (*Id.*)

C. The Clinical Application of Clopidogrel Bisulfate

Prior to the introduction of Plavix®, physicians prescribed aspirin and/or ticlopidine to prevent cardiovascular conditions believed to be caused or exacerbated by platelet aggregation. (Schneller Tr. 738-41.) The long-term use of aspirin is associated

with certain side effects, such as ulcers and gastrointestinal bleeding, and ticlopidine, as described above, is associated with an elevated risk of neutropenia and TTP. (Maffrand Tr. 1693-94; Schneller Tr. 763, 811-16.) Following its launch in 1998, Plavix® replaced ticlopidine as a prescription oral antiplatelet medication to a nearly complete extent. (Maffrand PI Tr. 155; Schneller Tr. 762, 806-07.)

Both prior to and since the launch of Plavix® on the market, large-scale clinical studies have been conducted involving clopidogrel. The results of the CAPRIE trial, published in 1996, showed that the long-term administration of Plavix® to patients with atherosclerotic vascular disease was more effective than aspirin in reducing the combined risk of ischemic stroke, myocardial infarction, or death caused by blockage of an artery. (Schneller Tr. 821-22.) Apotex's expert Dr. Stanley J.Schneller, a cardiologist, characterized the difference in efficacy as, however, "very modest." (Schneller Tr. 822.) CAPRIE also showed that Plavix® was associated with a low rate of neutropenia and TTP: only 0.1 percent of patients taking clopidogrel experienced neutropenia, and only 0.08 percent experienced neutropenia that was severe; no patient in the CAPRIE trial experienced TTP. (Schneller Tr. 812-817.) Dr. Schneller cautioned, however, that CAPRIE did not directly compare clopidogrel to ticlopidine; data derived from the CAPRIE study – when compared against historical data on ticlopidine – indicated a lower incidence of neutropenia and TTP with clopidogrel. (Schneller Tr. 812-13.)

Additional studies involving Plavix® included the CURE trial and the CLASSICS trial. The CURE trial, conducted between 1998 and 2000, demonstrated an 18.4% relative reduction in the risk of death, nonfatal myocardial infarction, or stroke in patients taking the combination of clopidogrel and aspirin versus patients taking aspirin alone. (Schneller Tr. 825.) Plavix® is also widely prescribed for patients who have received stents, the thin wire coils used to prop open arteries narrowed by arteriosclerotic plaque, to prevent thromboses that may form on the stents after their insertion. (Schneller Tr. 807-08, 811.) The CLASSICS trial demonstrated the superior safety of Plavix® compared to ticlopidine for stenting.

CONCLUSIONS OF LAW

I. *Infringement*

The parties have stipulated that Apotex's generic clopidogrel bisulfate product infringes Claim 3 of the '265 patent. That patent claims the "[h]ydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5(4,5,6,7-tetrahydro(3,2-c)thieno pyridyl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer," also known as clopidogrel bisulfate. ('265 patent at col. 12, ll. 37-41; *see also* Fact Stmt. at ¶¶ 18-19; May 7, 2004 Stipulation and Order.)

II. *Invalidity*

Having conceded infringement, Apotex bears the burden of proof because "[a] patent shall be presumed valid," and "[t]he burden of establishing invalidity of a patent or any claim thereof shall rest on

the party asserting such invalidity." 35 U.S.C. § 282. To overcome this presumption of validity at trial, "the party challenging a patent must prove facts supporting a determination of invalidity by clear and convincing evidence." *Schumer v. Lab. Computer Sys.*, 308 F.3d 1304, 1315 (Fed. Cir. 2002) (citing *Apotex USA, Inc. v. Merck & Co.*, 254 F.3d 1031, 1036 (Fed. Cir. 2001), *cert. denied*, 534 U.S. 1172, 122 S. Ct. 1196, 152 L. Ed. 2d 136 (2002)). As noted above, Apotex challenges the validity of the '265 patent on the grounds of anticipation, obviousness, and obviousness-type double patenting and challenges the enforceability of the '265 patent on the grounds that Sanofi engaged in inequitable conduct before the PTO. At trial, Apotex bore the burden of proving each of these defenses by clear and convincing evidence. *See Oney v. Ratliff*, 182 F.3d 893, 895 (Fed.Cir.1999) (invalidity); *Elk Corp. v. GAF Bldg. Materials Corp.*, 168 F.3d 28, 30 (Fed.Cir.1999) (unenforceability), *cert. denied*, 528 U.S. 873, 120 S. Ct. 178, 145 L. Ed. 2d 150 (1999). This is a "heavy burden," *Am. Hoist & Derrick Co. v. Sowa & Sons, Inc.*, 725 F.2d 1350, 1359 (Fed. Cir. 1984) (quoting *Radio Corp. of Am. v. Radio Eng'g Labs.*, 293 U.S. 1, 8, 54 S. Ct. 752, 79 L. Ed. 163 (1934)), because clear and convincing evidence "proves in the mind of the trier of fact 'an abiding conviction that the truth of [the] factual contentions [is] highly probable.'" *Intel Corp. v. U.S. Int'l Trade Comm'n*, 946 F.2d 821, 830 (Fed. Cir. 1991) (quoting *Colorado v. New Mexico*, 467 U.S. 310, 316, 104 S. Ct. 2433, 81 L. Ed. 2d 247 (1984)).

A. *Anticipation*

1. *Legal standard*

An invention may receive a patent unless "the invention was patented or described in a printed publication in this or a foreign country or in public use or sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102. *See Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302 (Fed. Cir. 1995) ("Invalidity based upon lack of novelty (often called 'anticipation') requires that the same invention . . . was known or used by others before it was invented by the patentee.") The application for the '265 patent was filed with the PTO on February 12, 1988, but claims priority from two French patent applications filed on February 17, 1987 and November 27, 1987, respectively. (Fact Stmt. at ¶ 9.) A patent is invalid due to anticipation when "each and every limitation is found either expressly or inherently in a single prior art reference." *See Celeritas Techs. Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998); *see also Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999 (Fed. Cir. 2006); *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003).

In addition, the prior art reference must be "an enabling disclosure," rather than mere "vague intimations of general ideas that may or may not be workable." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1366 (Fed. Cir. 1997) (citing *Brenner v. Manson*, 383 U.S. 519, 536, 86 S. Ct. 1033, 16 L. Ed. 2d 69 (1966)). "Accordingly, invalidity by anticipation requires that the four corners of a single, prior art

reference describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000). However, a disclosure is an "enabling disclosure" if a person of ordinary skill in the art "could have combined the publication's description of the invention with his own knowledge to make the claimed invention," *Impax Labs., Inc. v. Aventis Pharms., Inc.*, 468 F.3d 1366, 1381 (Fed. Cir. 2006) (quoting *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985)), and the fact "[t]hat some experimentation is required to practice the claimed invention is permissible, so long as it is not undue." *Moba, B.V. v. Diamond Automation, Inc.*, 325 F.3d 1306, 1321 (Fed. Cir. 2003).

2. *Discussion*

As a preliminary matter, the burden of showing invalidity is "especially difficult" when "the infringer attempts to rely on prior art that was before the patent examiner during prosecution." *See Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed. Cir. 2004) (citing *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999)). Here, not only was the prior art patent – the '596 patent – before the patent examiner during the prosecution of the '265 patent, but also the very same patent examiner, Bernard Dentz, approved both the '596 patent and the '265 patent.

a. *The '596 Patent Does Not Explicitly or Inherently Describe Clopidogrel Bisulfate*

Apotex relies on the '596 patent or its Canadian counterpart – the '875 patent – for its anticipation defense. The Court finds that Apotex has not proved by clear and convincing evidence that either patent describes clopidogrel bisulfate.

Claim 3 of the '265 patent, which claims clopidogrel bisulfate, reads as follows:

> Hydrogen sulfate of the dextro-rotatory isomer of methyl alpha-5 (4,5,6,7-tetrahydro (3,2-c) thienopyridl) (2-chlorophenyl)-acetate substantially separated from the levo-rotatory isomer.

'265 patent at col. 12. ll. 37-40. Thus, the claim consists of the following key limitations: (1) the bisulfate salt of (2) the dextrorotatory enantiomer of (3) the compound MATTPCA (4) substantially separated from the levorotatory enantiomer. (*See* Order dated May 7, 2004.)

Claim 2 of the '596 patent, in contrast, reads as follows:

> Methyl α-(4,5,6,7-tetrahydro-thieno(3,2,c)-5-pyridyl)-o.chlorophenyl-acetate.

'596 patent at col. 13, ll. 19-20. In the '596 patent specification, Claim 2 is exemplified as Example 1, which describes the hydrochloride salt of PCR 4099. '596 patent at col. 3, ll. 36-57.

In its decision affirming this Court's grant of a preliminary injunction in favor of Sanofi, the Federal Circuit found that "the plain language of claim 2 [of the '596 patent] only recites the free base,

MATTPCA, and does not expressly describe the dextrorotatory or levorotatory enantiomers or any salt. Because claim 2 [of the '596 patent] fails to describe each and every limitation of claim 3 [of the '265 patent] on its face, claim 2 does not anticipate claim 3." *Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1376 (Fed. Cir. 2006), *reh'g denied*, 2007 U.S. App. LEXIS 2807 (Fed. Cir. Jan. 19, 2007). Nothing in the trial record changes the plain language of the patents, and this Court therefore reaches the same conclusion on a complete record as this Court and the Federal Circuit reached on a more limited record: Claim 2 of the '596 patent does not expressly describe clopidogrel or its bisulfate salt.[9] The Court also finds that Example 1 does not expressly describe clopidogrel bisulfate – there is no explicit reference to the enantiomers of PCR 4099 in that example and the particular salt described is the hydrocholoride, not the bisulfate.

The more difficult question is whether the additional limitations – namely the dextrorotatory enantiomer and its bisulfate salt – are inherently described elsewhere in the '596 patent. "Inherent

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[9] That conclusion is supported by the absence from Claim 2 of the limitation which appears in Claim 1 – that the compounds within the genus "[include] both enantiomeric forms or their mixture." Because that language does not appear in Claim 2, it is appropriate to infer that Sanofi did not intend Claim 2 to cover the enantiomers of PCR 4099. *See Seachange Int'l, Inc. v. C-COR Inc.*, 413 F.3d 1361, 1368 (Fed. Cir. 2005) (quoting *Karlin Tech. Inc. v. Surgical Dynamics, Inc.*, 177 F.3d 968, 971-72 (Fed. Cir. 1999)) (applying "the common sense notion that different words or phrases used in separate claims are presumed to indicate that the claims have different meanings and scope").

anticipation requires that the 'missing characteristic is necessarily present, or inherent, in the single anticipating reference.'" *Glaxo Group*, 376 F.3d at 1348-49 (quoting *Schering Corp.*, 339 F.3d at 1377); *see also In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1349 (Fed. Cir. 2002) (quoting *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999)) ("Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.").

Claim 1 of the '596 patent claims a general formula and specifies that the compounds covered by that formula include:

> their addition salts with pharmaceutically acceptable mineral or organic acids . . . including both enantiomeric forms or their mixture.

'596 patent at col. 13, ll. 8-19. The parties have stipulated that clopidogrel bisulfate is a compound within the genus of Claim 1 of the '596 patent. (Fact Stmt. at ¶ 32.)

Claim 8, which is also relevant, reads as follows:

> A therapeutic composition having blood-platelet aggregation inhibiting activities and anti-thrombotic activities containing an effective amount of a compound of claim 1, or an addition salt thereof with a pharmaceutically acceptable mineral or organic acid or with mineral bases, or one of the two enantiomers or their mixture and a pharmaceutically acceptable carrier.

'596 patent at col. 14, ll. 5-11.

Apotex contends that importing the limitations of Claims 1 and 8 into Claim 2 or Example 1 of the specification discloses clopidogrel bisulfate to a person of ordinary skill in the art. Indeed, Claims 1 and 8 do make express reference to the claim limitations which are absent from Claim 2 – namely, that the invention disclosed by the '596 patent includes the enantiomers of each racemic mixture and their formulation as pharmaceutically acceptable salts. Furthermore, some of the examples set forth in the specification – albeit not Example 1, which discloses PCR 4099 – are formulated as bisulfate salts.

Apotex's argument, however, is ultimately unpersuasive. First, it is undisputed that "[a] prior art reference that discloses a genus still does not inherently disclose all species within that broad category." *Metabolite Labs., Inc. v. Lab. Corp. of Am. Holdings*, 370 F.3d 1354, 1367 (Fed. Cir. 2004); *see also Atofina*, 441 F.3d at 999. In essence, patentability is not precluded by the fact that an inventor has identified or selected a single compound with particularly desirable qualities from a large class of previously patented compounds. *See Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 897 (S.D. Ind. 2005) ("Inventions based on the identification or selection of a specific material or compound with particularly desirable properties within a previously disclosed genus of such materials or compounds do not violate any of the substantive requirements for patentability.") Although clopidogrel bisulfate concededly falls into the broad genus disclosed by Claims 1 and 8 – a genus which includes millions of possible compounds – a person of ordinary skill in the art would need to engage in impermissi-

ble "mechanistic dissection and recombination" of those disparate elements to arrive at the particular combination that is clopidogrel bisulfate. *In re Ruschig*, 343 F.2d 965, 974 (C.C.P.A. 1965); *see also Zenith Goldline*, 364 F. Supp. 2d at 900.

As noted above, Claim 2 describes the free base of PCR 4099 and Example 1 depicts PCR 4099 as a hydrochloride salt. However, neither of these disclosures describes the enantiomers of the racemate. *See Pfizer Inc. v. Ranbaxy Labs. Ltd.*, 405 F. Supp. 2d 495, 519 (D. Del. 2005), *aff'd in part, rev'd in part on other grounds*, 457 F.3d 1284 (Fed. Cir. 2006) (noting that "courts considering issues related to racemates and their individual isomers have concluded that a prior art disclosure of a racemate does not anticipate the individual isomers of the racemate"); *In re May*, 574 F.2d 1082, 1090 (C.C.P.A. 1978) ("[T]he novelty of an [enantiomer] is not negated by the prior art disclosure of its racemate.").

Despite the fact that the '596 patent covers millions of possible compounds when taking into account the full range of possible addition salts, Apotex invokes *In re Petering*, 301 F.2d 676 (C.C.P.A. 1962), and *In re Schaumann*, 572 F.2d 312 (C.C.P.A. 1978) in support of the proposition that the '596 patent would be read by a person of ordinary skill in the art to describe a dramatically smaller genus of nine preferred compounds, including clopidogrel bisulfate.

In *Petering*, the Court of Customs and Patent Appeals upheld a Patent Board decision which had found that a claim covering several specific chemical compounds was anticipated by a prior art patent that had disclosed a class of compounds of which the spe-

cific compounds were members. 301 F.2d at 682. To reach that conclusion, the court identified "specific preferences" in the prior art patent that narrowed the generic formula to a limited subclass of approximately twenty compounds. *Id.* at 681. That same court reached a similar conclusion on similar facts in *Schaumann*, again noting the presence of a disclosed preference in the prior art patent. 572 F.2d at 316. *Petering* and *Schaumann* thus stand for the proposition that a genus may be small enough that its disclosure is equivalent to the description of each species within it. *See Petering*, 301 F.2d at 681-82; *Schaumann*, 572 F.2d at 316-17.

Apotex's proposed "sub-genus" consists of PCR 4099 and its levorotatory and dextrorotatory enantiomers, as well as three possible addition salts – the hydrobromide, the hydrochloride, and the bisulfate. This results in a subset of nine possible combinations out of the millions of combinations otherwise covered by the general formula disclosed in Claim 1 of the '596 patent. Apotex, however, has not persuaded the Court that the specification and claims of the '596 patent would have guided a person of ordinary skill to that particular subset.

First, Apotex contends that the pharmacological testing data in the '596 patent points a person of ordinary skill in the art directly to PCR 4099 and its enantiomers. That proposition, however, is undermined by several of this Court's findings. Most importantly, the testing data relied on by Apotex is based on screening tests that do not provide precise or sophisticated data. The tests did not, for example, involve a sufficient variety of doses of each compound from which ED_{50} values could be calculated. A person

of ordinary skill in the art would not use that data to rank the tested compounds against each other as a means of evaluating pharmacological activity, except where a particular compound showed virtually no platelet inhibition activity.

Furthermore, although PCR 4099 performed well in all four tests, other compounds also performed as well or, arguably, better, on one or more of the tests. Certainly, the results did not rule out the potential development of every other compound exemplified in the '596 patent apart from PCR 4099. The Court also notes that nothing in the '596 patent would have taught a person of ordinary skill in the art which of the tested compounds was the least toxic or best tolerated in animals or humans. The '596 patent specification describes all the compounds of the invention as exhibiting "an excellent tolerance and low toxicity." '596 patent at col. 8, ll. 41-49. That data, therefore, fails to support the proposition that the testing data disclosed in the '596 patent singles out PCR 4099 – and, by extension, its enantiomers – as the "specific preferences" of the inventors. Accordingly, the '596 patent would not direct a person of ordinary skill in the art to a "sub-genus" consisting of PCR 4099 and its enantiomers.[10]

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[10] The fact that Sanofi publicized PCR 4099 at the San Diego and Jerusalem conferences in 1985 is inapposite for purposes of Apotex's contention that a person of ordinary skill in the art would have viewed PCR 4099 and its enantiomers as a subgenus. Anticipation requires that the claimed invention be described in a single, prior art reference; the disclosures of multiple references may not be combined. *See Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.*, 726 F.2d 724, 726-27 (Fed. Cir. 1984).

Second, Apotex contends that the examples in the '596 patent specification make clear that the three most likely salts forms would have been the hydrobromide, the hydrochloride, and the bisulfate. That contention is undermined by the fact that the person of ordinary skill in the art recognizes that there is no necessary correlation between the use of a particular pharmaceutically acceptable acid to form a crystalline salt with a racemate, on one hand, and the choice of acid to be used for the formation of a crystalline salt of the corresponding enantiomer, on the other. Thus, the fact that certain acids were used to purify the compounds exemplified in the '596 patent would not lead the person of ordinary skill in the art to a limited sub-genus involving only three salts. Although certain acids might – for a variety of reasons – be better candidates than others to use for the formulation of a pharmaceutical salt, the prior art would not have limited the choice of likely acids to only those three acids asserted by Apotex.

Accordingly, the full trial record compels the conclusion that the '596 patent does not direct a person of ordinary skill in the art exclusively to PCR 4099, its enantiomers, and three particular salt forms. In sum, the '596 patent does not inherently disclose clopidogrel bisulfate.

For largely the same reasons, the Canadian '875 patent does not describe clopidogrel bisulfate. The main distinction between the '875 patent and the '596 patent is that the former includes the language that "if desired," the enantiomers of any compound covered by the general formula may be isolated and prepared as a salt. This does nothing, however, to narrow the universe of possible compounds to the bi-

sulfate salt of the dextrorotatory enantiomer of a particular racemate – MATTPCA. Accordingly, the '875 patent also does not describe clopidogrel bisulfate.

b. *The '596 Patent Does Not Enable a Person of Ordinary Skill in the Art to Practice Clopidogrel Bisulfate Without Undue Experimentation*

Because the '596 patent does not expressly or inherently describe clopidogrel bisulfate, the Court need not determine whether the prior art patent enabled its practice. Nonetheless, even if one impermissibly engaged in "mechanistic dissection and recombination" of the various claims and examples of the '596 patent to piece together the elements of clopidogrel bisulfate, *see Ruschig*, 343 F.2d at 974, the Court finds that that patent did not enable a person of ordinary skill in the art "to practice the invention without undue experimentation." *Advanced Display Sys.*, 212 F.3d at 1282. *See Impax Labs.*, 468 F.3d at 1383 ("When a reference discloses a class of compounds, i.e., a genus, a person of ordinary skill in the art should be able to at once envisage *each member* of th[e] . . . class for the individual compounds, i.e. species, to be enabled.") (internal quotations omitted) (emphasis in original); *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1355 (Fed. Cir. 2003) (finding that even if a presumption of enablement arises from the fact that a claimed compound falls within the genus of a prior art patent, the patentee can adduce evidence to prove that the disclosure is not enabling).

There is no serious dispute between the parties that a person of ordinary skill in the art for these purposes has a bachelor's degree in chemistry with a specialization in organic chemistry and would have several years experience in the field involved in the synthesis, study and properties of drugs, drug candidates, and biologically active compounds. This person would have both knowledge and experience in the preparation and separation of stereoisomers.

First, the '596 patent did not disclose to a skilled person how the enantiomers of PCR 4099 could be separated. Nothing in the prior art patent suggests, for example, that diastereomeric salt formation is the preferred means of obtaining the enantiomers of the racemic mixtures covered by the general formula of Claim 1. Although there were as many as ten different methods that a chemist might use to obtain the enantiomers of a racemate in 1987, the evidence proved that even if some of those methods could be immediately eliminated from consideration, there was no way to know which particular method or methods of the remaining options would be successful with a particular racemate. A chemist cannot be certain which method of separation or synthesis – or what configuration of variables presented by a particular method – will be effective for a given compound. Although the Canadian '875 patent states that "if desired" one can separate the enantiomers of the claimed compounds or make a salt, that statement does not demonstrate that undue experimentation would not be required to implement that suggestion. Discovering which method and what combination of variables is required is sufficiently arduous and uncertain as to require undue experimentation.

even by one skilled in the relevant art. While not entirely dispositive, it is noteworthy that Sanofi – whose chemists were highly sophisticated and well-trained in the relevant art – spent a considerable amount of time trying to obtain the enantiomers of PCR 4099. If the '596 patent enabled clopidogrel, Sanofi would most certainly not have recorded numerous failed attempts using a variety of methods before attempting diastereomeric salt formation and obtaining the enantiomers.

Second, there is evidence, which is credited, that even if the enantiomers of a racemic mixture are obtained, a person of ordinary skill in the art must often experiment at length to formulate a suitable, crystalline salt when the prior art provides no guidance regarding what salt form of a particular compound will possess the required properties – the exact situation that confronted Sanofi in this case. As noted, the '596 patent provided no specific guidance that would have led a person of ordinary skill to prepare a methyl ester, or any enantiomer, as a bisulfate salt. Although the prior art – as a general matter – would have pointed a person of ordinary skill in the art to the universe of pharmaceutically acceptable acids, there are sufficient additional factors – including the risk that attempting to form a salt with certain acids will lead to racemization of the compound – such that the Court finds that preparing the free base of clopidogrel as a bisulfate salt also would have required a level of experimentation that was undue.

3. *Conclusion*

In view of the evidence and the applicable law, neither of the prior art patents – the '596 patent and its Canadian counterpart, the '875 patent – explicitly or inherently described the invention disclosed by Claim 3 of the patent-in-suit. Although the benefit of hindsight permits one to pull together the various claim limitations of clopidogrel bisulfate from the '596 patent or the '875 patent, these disparate references in each patent do not as a matter of law or fact anticipate the precise combination of elements described by Claim 3 of the '265 patent. Furthermore, neither the '596 patent nor the '875 patent provides specific guidance regarding how to obtain the enantiomers of any racemate covered by Claim 1, including PCR 4099, nor how to select a particular pharmaceutically acceptable acid to create a suitable salt form of a particular enantiomer. In sum, neither the '596 patent nor the Canadian '875 patent invoked by Apotex enable a person of ordinary skill in the art to practice the invention disclosed by the patent-in-suit without undue experimentation. Accordingly, Apotex has failed to show by clear and convincing evidence that clopidogrel bisulfate is anticipated by the '596 patent.

B. *Obviousness*

1. *Legal Standard*

A patent may not be obtained "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art." 35 U.S.C. § 103. "Obviousness is a question of law which is predicated upon

several factual inquiries." *Ranbaxy Labs.*, 405 F. Supp. 2d at 516. To assess whether an invention is obvious, the Court considers: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the art; and (4) objective evidence, or "secondary considerations," of nonobviousness, such as "commercial success, long felt but unsolved needs, [or] failure of others." *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966). To this end, "mere identification in the prior art of each element is insufficient to defeat the patentability of the combined subject matter as a whole. Rather, a party alleging invalidity due to obviousness must articulate the reasons one of ordinary skill in the art would have been motivated to select the references and to combine them." *Abbott Labs. v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1336 (Fed. Cir. 2006) (quoting *In re Kahn*, 441 F.3d 977, 986 (Fed. Cir. 2006)).

Moreover, it is not enough for Apotex to have shown that the combination of claim limitations found in Claim 3 of the '265 patent would have been "obvious to try." *See In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995) ("A general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out."); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 725 (Fed. Cir. 1990) ("[W]e have consistently held that 'obvious to try' is not to be equated with obviousness under 35 U.S.C. § 103."). Rather, to establish obviousness, "a claimed *specific* compound" must be "precisely envisioned" by the prior art. *Deuel*, 51 F.3d at 1559 (emphasis in original). To

make that determination, the Court must assess, without the benefit of hindsight, whether the prior art would have suggested to a person of ordinary skill in the art that the invention should be made and that it would have a "reasonable likelihood of success." *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

In addition, "[t]he proper approach to the obviousness issue must start with the claimed invention *as a whole.*" *Kimberly-Clark Corp. v. Johnson & Johnson*, 745 F.2d 1437, 1448 (Fed. Cir. 1984) (emphasis in original). Where the claimed invention is a chemical compound, the "compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). This principle requires the Court to determine whether clopidogrel bisulfate – including its properties – would have been obvious to a person of ordinary skill in the art as of February 17, 1987, the date on which the first French patent application for clopidogrel bisulfate was filed. Evidence that the compound exhibited unexpected or surprising properties rebuts a finding of prima facie obviousness. *In re Dillon*, 919 F.2d 688, 696 (Fed. Cir. 1990).

2. *Discussion*

According to Apotex, clopidogrel bisulfate was rendered obvious by the '596 patent because, after gaining familiarity with that patent, a person of ordinary skill in the art would have viewed as obvious the active enantiomer of PCR 4099 in the form of each of the three salts used for ester compounds in the examples of the '596 patent – namely, the hydro-

chloride, bisulfate and hydrobromide. Apotex also contends that a person of ordinary skill would have known that PCR 4099 held the most promise among the compounds disclosed by the '596 patent, a conclusion that would have been bolstered by Sanofi's own efforts to publicize PCR 4099 in the scientific community. A person of ordinary skill would also have known, in Apotex's view, that separating the enantiomers of PCR 4099 would elicit one active and one inactive enantiomer and that the enantiomer that exhibited antiplatelet activity would also be better tolerated. The person of ordinary skill in the art also would have viewed as obvious the preparation of that active enantiomer of PCR 4099 as each of the disclosed salt forms. Moreover, the '596 patent expressed the purpose behind the exercise – the search for a platelet aggregation inhibitor with a better activity/toxicity ratio than other drugs currently on the market. Thus, according to Apotex, the '596 patent also provided the motivation for a person of ordinary skill to synthesize clopidogrel bisulfate. Apotex further contends that regulatory trends in the mid-1980s favoring the development of enantiomers rather than their racemic mixtures – a trend that was forecasted by the prior art – provided additional motivation.

In sum, Apotex contends that the evidence demonstrates a prima facie case of obviousness. Indeed, in the case of chemical compounds where the prior art is "close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art compound(s), then there arises what has been called a presumption of obvi-

ousness or a prima facie case of obviousness." *Dillon*, 919 F.2d at 696. "[E]ven though a patentee never must submit evidence to support a conclusion by a judge or jury that a patent remains valid, once a challenger introduces evidence that might lead to a conclusion of invalidity – what we call a prima facie case – the patentee 'would be well advised to introduce evidence sufficient to rebut that of the challenger.'" *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360 (Fed. Cir. 2007) (quoting *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 806 F.2d 1565, 1570 (Fed. Cir. 1986)). Rebuttal evidence may consist of "a comparison of test data showing that the claimed composition[] possess[es] unexpectedly improved properties or properties that the prior art does not have." *Dillon*, 919 F.2d at 692-93. An "unexpected result" includes "some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Obviousness can also be rebutted by showing that "the prior art teaches away from the claimed invention." *In re Geisler*, 116 F.3d 1465, 1471 (Fed. Cir. 1997).

The Court, therefore, must first consider whether Apotex has established a prima facie case of obviousness based on the prior art and, if so, whether Sanofi has effectively rebutted that presumption on the basis of the evidence submitted. For purposes of analysis, the Court assumes that Apotex has made a prima facie case of obviousness of the dextrorotatory enantiomer of PCR 4099 in view of the disclosure of the racemate in the '596 patent and the prior art teachings that (1) racemic compounds may be sepa-

rated into their enantiomers; and (2) those enantiomers, if obtained, may exhibit different biological activity or different degrees of the same type of biological activity exhibited by the racemate. Thus, the analysis will proceed directly to whether the specific properties exhibited by clopidogrel bisulfate-the invention, as a whole – would have been unexpected to a person of ordinary skill in the art.

Because a compound and its properties are one and the same, *see Papesch*, 315 F.2d at 391, evidence of the fact that any property of clopidogrel bisulfate is unexpected – as compared to PCR 4099 or anything else in the prior art – rebuts the presumption that clopidogrel bisulfate is obvious in view of its racemate. *See Ortho-McNeil Pharm., Inc. v. Myland Labs., Inc.*, 348 F. Supp. 2d 713, 760-61 (N.D. W. Va. 2004); *May*, 574 F.2d at 1092-93. In this regard, the Court concludes that the prior art did not enable a person of ordinary skill in the art to predict with a reasonable expectation of success whether one enantiomer of PCR 4099 would have better pharmaceutical properties than the racemate itself, whether one enantiomer would have all of the activity and none of the toxicity of the racemate as a whole, or whether a single enantiomer would have both all of the activity and all of the toxicity. Moreover, the prior art would not have made obvious whether an isolated enantiomer of PCR 4099 would racemize in the body, serving to neutralize the gains achieved by separating the enantiomers.

Apotex contends that clopidogrel's lack of neurotoxicity should not be viewed as unexpected because Sanofi – prior to filing the application for the '265 patent – had not disclosed its internal testing

data which showed that PCR 4099 had a tendency to cause convulsions in animals. Moreover, Sanofi had publicized that PCR 4099 exhibited good tolerance and had even conducted human trials with the racemate. Apotex's argument, however, misapprehends the role of "unexpected properties" in the analysis of obviousness. To determine whether a given compound is obvious compared to a prior art compound, any and all properties of those compounds must be considered, even where the prior art has not disclosed the relevant properties of the prior art. *See Zenith Goldline*, 471 F.3d at 1378; *In re Lunsford*, 327 F.2d 526, 528 (C.C.P.A 1964).

Evidence of the course of Sanofi's research prior to securing the '265 patent also weighs in favor of the conclusion that separating the enantiomers of PCR 4099 would not have been obvious to a person of ordinary skill in the art at the relevant time. *See Dow Chem.*, 837 F.2d at 473; *Rosemount, Inc. v. Beckman Instruments, Inc.*, 727 F.2d 1540, 1544 (Fed. Cir. 1984). Sanofi spent four years and "tens of millions of dollars" developing and extensively testing the racemate PCR 4099 before deciding to try separating the enantiomers of the racemic mixture. (Maffrand PI Tr. 144.) The superiority of clopidogrel to PCR 4099 – which was only confirmed later – was clearly not obvious to the chemists at Sanofi. Apotex has not made a persuasive case to provide an explanation as to why the skilled chemists at Sanofi, furthermore, would have acted – as Apotex contends – so contrary to the hypothetical person of ordinary skill in the art.

Furthermore, the fact that the formulation of clopidogrel as a bisulfate salt results in a pharmaceutical compound possessing a highly favorable

combination of properties would also not have been obvious to a person of ordinary skill. There is undisputed testimony from experts for both sides that the bisulfate salt of clopidogrel has a highly favorable combination of properties: a high melting point, long-term stability, non-hygroscopic, and good solubility. Furthermore, the bisulfate salt was the *only* salt obtained by Sanofi that demonstrated that favorable combination of properties. That result was unexpected.

Apotex contends that a very recent decision of the Federal Circuit, *Pfizer, Inc. v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007), *reh'g denied*, 2007 U.S. App. LEXIS 11886 (Fed. Cir. May 21, 2007), compels a different conclusion in this case. The Court, however, finds that *Pfizer* is distinguishable from this case. In *Pfizer*, the invention was the "besylate" salt of the antihypertensive drug amlodipine. 480 F.3d at 1352. Amlodipine had been specifically described in a prior Pfizer patent, and that prior art patent had described twelve illustrative pharmaceutically acceptable acid addition salts. *Id.* at 1353. The maleate was listed as the "preferred" salt and amlodipine was exemplified in that form in the prior art patent. *Id.* After obtaining that patent, however, Pfizer discovered that the maleate salt, for unforeseen reasons, was not suitable for the commercial manufacture of tablets due to stickiness and tablet degradation. *Id.* at 1353-54. The chemists at Pfizer attributed those problems to the particular chemical structure of the maleate salt – a reactive double bond in the maleate anion – which made the salt susceptible to degradation. *Id.* at 1362. Based on that knowledge, Pfizer chemists compiled a list of

seven salts, including besylate, which lacked the problematic double bond. *Id.* at 1354. After testing the various options, the besylate salt was found to be the most suitable alternative to the maleate. *Id.*

The Court finds, however, that *Pfizer* does not support the proposition that it would have been obvious to a person of ordinary skill in the art to formulate clopidogrel as a bisulfate salt. First, the chemists in *Pfizer* were able to identify the structural feature of the maleate salt that was causing problems, and, with that knowledge, were able to produce a short list of salts that they expected to solve the problem. In this case, importantly and by contrast to the situation in *Pfizer*, there were no structural features that would have guided Sanofi chemists in avoiding or selecting any specific acid.

Second, in *Pfizer*, the Federal Circuit noted that several prior art references, including patents, specifically suggested to a person of ordinary skill in the art that the use of the besylate salt would offer improved stability in the particular compound at issue. *Id.* at 1363. The Federal Circuit emphasized that the nature of the prior art in that case was such that the role of testing – after Pfizer chemists had identified the besylate salt as an option that they expected to succeed – was simply to verify the expected physicochemical characteristics of the salts identified. *Id.* at 1366-67. Here, there was no prior art teaching that the bisulfate salt was particularly likely to be a successful salt form of clopidogrel, and additional prior art – such as the Gould reference – might actually have led the person of ordinary skill in the art away from sulfuric acid, at least as an initial matter.

For these reasons and based on the findings of fact with respect to preparation of clopidogrel as a bisulfate salt, this Court concludes that *Pfizer* – which the Federal Circuit emphasized rested on its "particularized facts," *id.* at 1367 – does not control under the "particularized facts" of this case. Accordingly, the unexpected success of the bisulfate salt of clopidogrel – especially taking into account the lack of prior art directing a person of ordinary skill in the art to that particular outcome – independently supports the conclusion that Claim 3 of the '265 patent is non-obvious over the prior art.

As noted above, courts must also consider objective indicia, or "secondary considerations," of nonobviousness. *See Graham*, 383 U.S. at 17-18; *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667-68 (Fed. Cir. 2000). Whether an invention fulfills a "long-felt but unsolved" need, *see Graham*, 383 U.S. at 17-18, 35-36, was the only secondary consideration on which the parties offered extensive evidence in this case. At trial, the parties presented conflicting evidence regarding whether a long-felt need existed in the market for a more effective and safer platelet aggregation inhibitor and, more particularly, whether Plavix® filled that need. The Court need not resolve that debate. As this Court found following the preliminary injunction hearing, Sanofi's ownership of the '596 patent precluded anyone else from bringing clopidogrel bisulfate to market throughout the duration of that patent. For that reason, evidence relating to the "failure of others," a "long-felt but unsolved need," the "commercial success" of Plavix® – a factor on which the parties expressly did not present evidence at trial – and "copy-

ing" is undermined by the fact that those phenomena – to the extent they exist in this case – could have been derived from Sanofi's ownership of the '596 patent as much as from the nonobviousness of clopidogrel bisulfate. *See, e.g.*, *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (the inference drawn from a product's commercial success fails when others are legally barred from testing or practicing the invention given the existence of another patent covering that invention.) Although the Court has considered these secondary factors of nonobviousness – to the extent they were asserted by the parties at trial or find support in the record – the Court concludes that they do not relate to obviousness in this particular case.

3. *Conclusion*

This Court concludes that Sanofi has effectively rebutted a prima facie case of obviousness by demonstrating that clopidogrel bisulfate – as a whole – possesses unexpected properties that could not have reasonably been viewed as a likely outcome of preparing the invention. Whether or not it may have been "obvious to try" separating the enantiomers of PCR 4099 and, secondarily, preparing its dextrorotary enantiomer as a bisulfate salt, the wide range of possible outcomes and the relative unlikelihood that the resulting compound would exhibit the maximal increase in antiplatelet aggregation activity and the absence of neurotoxicity makes clopidogrel bisulfate non-obvious. Sanofi's discovery that the bisulfate form of clopidogrel – a combination that the prior art did not predict would yield a Tier 3 salt with a highly desirable combination of properties – is an additional

basis for concluding the clopidogrel bisulfate was non-obvious on the relevant date.

C. *Double-Patenting*

The judicial doctrine of obviousness-type double-patenting prevents a patent claim from validly issuing when it "is obvious over, or anticipated by" a claim in an earlier patent. *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 968 (Fed. Cir. 2001). It is a "judge-made criterion adopted out of necessity where the courts were faced with a situation in which claims in two applications or patents were not drawn precisely to the *same* invention, but were drawn to inventions so very much alike as to render one obvious in view of the other and to effectively extend the life of the patent that would have [had] the earlier of the two issue dates." *Gerber Garment Tech., Inc. v. Lectra Sys., Inc.*, 916 F.2d 683, 686 (Fed. Cir. 1990) (emphasis in original).

The test for obviousness-type double-patenting is narrower than the statutory obviousness inquiry pursuant to 35 U.S.C. § 103. *See Geneva Pharms., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1378 (Fed. Cir. 2003) ("Obviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application."); *Affymetrix, Inc. v. Pe Corp.*, 01 Civ. 0634, 2002 U.S. Dist. LEXIS 24649, at *5 n.3 (S.D.N.Y. Dec. 24, 2002) ("The same type of analysis is used for an obviousness-type double patenting inquiry as for a Section 103 obviousness inquiry, except that the scope of a double patenting inquiry is limited to only the claims

of the first patent, rather than the entirety of its disclosure.").

The double-patenting inquiry is subsumed by the broader statutory inquiry pursuant to 35 U.S.C. § 103 because Sanofi's entire '596 patent was prior art at the time the '265 patent issued. Because Apotex has failed to prove at trial that the '265 patent was obvious in light of the '596 patent as a whole, it has also necessarily failed to prove that the '265 patent was obvious in light of the specific claims of the '596 patent.

III. *Unenforceability Due to Inequitable Conduct Before the PTO*

Apotex contends that the '265 patent is unenforceable due to inequitable conduct by Sanofi when the patent was prosecuted before the PTO.

A. *Legal Standard*

"To hold a patent unenforceable for inequitable conduct, a court must find, by clear and convincing evidence, that the applicant omitted or misrepresented material facts with the intention of misleading of deceiving the patent examiner." *Monsanto Co. v. Bayer BioScience N.V.*, 363 F.3d 1235, 1239 (Fed. Cir. 2004). Both materiality and intent are questions of fact. *See Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1324 (Fed. Cir. 2000). Pursuant to 37 C.F.R. § 1.56, as in effect in 1988, certain individuals associated with the application for a patent have a duty of candor and good faith toward the PTO, which includes the duty to disclose to the PTO "information they are aware of which is material to the examination of the application." A breach of this duty

may constitute inequitable conduct rendering the patent unenforceable.

To demonstrate a failure to disclose material information, the party asserting inequitable conduct must show "(1) prior art that was material; (2) knowledge chargeable to an applicant of that prior art and of its materiality; and (3) failure of the applicant to disclose the art resulting from an intent to mislead the PTO." *Elk Corp.*, 168 F.3d at 30. Proof of inequitable conduct can be rebutted by "a showing that (a) the prior art was not material, (b) if the prior art was material, a showing that the applicant did not know of that art; (c) if the applicant did know of the art, a showing that the applicant did not know of its materiality; or (d) a showing that the applicant's failure to disclose the art did not result from an intent to mislead the PTO." *Id.* at 30.

"Information is 'material' when there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent." *Id.* at 31. "[A]n otherwise material reference need not be disclosed if it is merely cumulative of or less material than other references already disclosed." *Id.*

With regard to intent to deceive the PTO, the Court must infer intent from the facts and circumstances surrounding Sanofi's overall conduct. *See Paragon Podiatry Lab., Inc. v. KLM Labs., Inc.*, 984 F.2d 1182, 1190 (Fed. Cir. 1993). However, the Court will not infer intent to deceive without clear and convincing evidence. *See Baxter Int'l Inc. v. McGaw, Inc.*, 149 F.3d 1321, 1329 (Fed. Cir. 1998) ("[T]here must

be clear and convincing evidence that the applicant made a deliberate decision to withhold a known material reference."); *Old Town Canoe Co. v. Confluence Holdings Corp.*, 448 F.3d 1309, 1322 (Fed. Cir. 2006) (affirming district court's finding of no intent to deceive when party did "little more than urge this court to draw an inference of intent to deceive, arguing that the applicant or his attorney knew, or should have known that withheld information would be material").

B. *Discussion*

Apotex alleges that Sanofi made materially false statements and omitted material facts in an intentional effort to deceive the PTO examiner. Apotex first claims that Sanofi falsely represented to the PTO that the therapeutic activity of the dextrorotatory enantiomer was "unexpected." Second, Apotex asserts, Sanofi falsely informed the PTO examiner that the relative levels of tolerance between the dextrorotatory and levorotatory enantiomers were surprising. Finally, Sanofi allegedly concealed that Dr. Maffrand was a true inventor of clopidogrel. Because, Apotex contends, Sanofi failed to name Dr. Maffrand as an inventor in the '265 patent, it was able to conceal both his knowledge that there was nothing unexpected about the properties of clopidogrel as well as the 1984 journal article co-authored by Dr. Robert Colman on this topic that Maffrand knew about and that allegedly should have been submitted as relevant prior art. Taking each of these allegations in turn, the Court concludes that Apotex has failed to prove by clear and convincing evidence that Sanofi engaged in inequitable conduct when prosecuting the '265 patent before the PTO.

1. *"Unexpected" Therapeutic Activity*

Apotex has not proven that Sanofi misled the examiner when it stated: "In an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive. Moreover, the inactive levo-rotatory enantiomer I_l is the less well tolerated of the two enantiomers." (Def. Ex. 9 at CLO-DRL 51362.)

As the Court concluded above, the properties of the dextrorotatory enantiomer of PCR 4099 were, taken together, unexpected in light of the prior art. Apotex contends that Sanofi's characterization of the therapeutic properties of clopidogrel as "unexpected" was false in light of Sanofi's prior work on thienopyridine compounds. The Court finds, however that, Sanofi's internal, non-public test data – particularly regarding PCR 1033 and its enantiomers – was not material. First, those results were non-public and not part of the prior art, and, therefore, could not effect the examiner's determination of whether clopidogrel bisulfate exhibited unexpected properties in light of the prior art. Even if that data had been disclosed, moreover, it did not provide any firm basis on which a person of ordinary skill in the art could reasonably have predicted the likely results of separating the enantiomers of PCR 4099 and preparing the active enantiomer as a bisulfate salt. If Sanofi had disclosed its conflicting data relating to both PCR 1033 and PCR 3549 – where the enantiomers of the former exhibited different levels of activity and the enantiomers of the latter exhibited equivalent activity – this would have confirmed that a skilled chemist would not have known *ex ante* whether PCR

4099's enantiomers would exhibit a significant split in therapeutic activity and toxicity.

Apotex also points to the written comments from Sanofi's French patent agent Jacqueline LaForest in 1987 as she helped to prepare the application for the French patent on clopidogrel bisulfate. Ms. LaForest replied to a draft of the French patent application with the handwritten remark, "[t]he pharmacology study does not lead to surprising activity; we will not pass the examiner's hurdles without other results." (Def. Ex. 304.) Apotex alleges that this remark can only be taken as a reply to the draft phrase, "[i]n an unexpected manner only the dextro-rotatory enantiomer I_d exhibits a platelet aggregation inhibiting activity, the levo-rotatory enantiomer I_l being inactive." However, LaForest's comments were made in January 1987, before the results of March 1987 toxicology studies were known. These toxicology studies revealed what was – for purposes of review by the PTO – "unexpected" about clopidogrel, and that was the complete decoupling of therapeutic activity and neurotoxicity between the two enantiomers of the racemate. In addition, Laforest commented on the pharmacological activity yet also believed – mistakenly – that the relevant test results were not part of the application. As noted above, those very results in fact appeared in the draft application. Accordingly, the Court cannot credit Laforest's comment regarding a perceived lack of "surprising activity" in support of Apotex's allegations of inequitable conduct.

With respect to the memorandum from Michel de Haas dated December 30, 1986, the Court notes that these comments were made over a year after Dr. Maffrand first asked Badorc to pursue the isolation

of the enantiomers of PCR 4099 and nearly a month after Fréhel had already circulated his first draft of the French patent application for clopidogrel bisulfate – a draft in which the phrase "[i]n an unexpected manner" already appeared. Haas' speculation that the active enantiomer might offer a "major therapeutic advantage" was subsequently confirmed by the results of toxicology testing, which demonstrated that virtually all of the neurotoxicity associated with PCR 4099 was located in the inactive levorotatory enantiomer. Accordingly, the Court finds that the Haas memorandum fails to provide convincing evidence of any intent to mislead the PTO by inserting the phrase "[i]n an unexpected manner . . ." If anything, the Haas memorandum is simply a correct statement of the principle that the patentability of the dextrorotatory enantiomer depended on its unexpected properties – and the Court finds that those properties were, in fact, unexpected and discovered by Sanofi prior to the date that the U.S. patent application for clopidogrel bisulfate was filed.

2. *Tolerance*

Apotex's second allegation of inequitable conduct before the PTO concerns Sanofi's statement regarding the relative levels of tolerance between the dextrorotatory and levorotatory enantiomers. Apotex asserts that Sanofi in fact had not conducted any tolerance testing at the time of the U.S. patent application, and thus had no data to support any assertions regarding how well clopidogrel was tolerated.

However, at the time of its '265 patent application, Sanofi had evidence from pharmacological and

toxicity studies that was relevant to how well clopidogrel was tolerated. Apotex primarily contends that the prior art recognizes a distinction between tolerance and toxicity. The record shows, however, that – at a minimum – the terms are closely related and are often used interchangeably, both at Sanofi and elsewhere. Furthermore, the Court finds that the patent examiner, Bernard Dentz, viewed the toxicity data included in the patent application as a sufficient basis for the statement that the levorotatory enantiomer was "less well tolerated" than clopidogrel. This strongly supports the Court's conclusion that the examiner was not misled by Sanofi's usage of the term "less well tolerated" in the patent application itself.

Apotex also relies on *Hoffmann-La Roche, Inc. v. Promega Corp.*, 323 F.3d 1354, 1363-65 (Fed. Cir. 2003), and *Purdue Pharma L.P. v. Endo Pharmaceuticals Inc.*, 438 F.3d 1123, 1129-33 (Fed. Cir. 2006), to suggest that the accuracy of the statement depended exclusively on the existence of test data predating Fréhel's drafting of the original French patent application. But Apotex's reliance on those cases is misplaced. In those cases, unlike here, the patentees had made assertions about the properties of their inventions in the past tense – not the present – implying that they were relying exclusively on data obtained before the assertion was made. In this case, the data supporting the statement in the '265 patent application was presented in Table IV of the application, and Sanofi obtained additional data supporting the statement both before and after it applied for the U.S. patent.

In sum, there is no substantial evidence that any person with a duty of candor intended to mislead the examiner by describing the levorotatory enantiomer as less well-tolerated than clopidogrel. Indeed, there is no evidence that the examiner was misled.

3. *Dr. Maffrand's Knowledge*

Apotex's third inequitable conduct allegation is that Sanofi concealed that Dr. Maffrand was a true inventor of clopidogrel bisulfate, and that concealing his status facilitated Sanofi's concealment of his knowledge that there was nothing unexpected about the properties of clopidogrel, based on his prior work with PCR 1033. Withholding Dr. Maffrand's name, Apotex argues, enabled Sanofi to conceal a prior art journal article by Robert W. Colman and William R. Figures entitled "Characteristics of an ADP Receptor Mediating Platelet Activation" of which Maffrand was aware. Apotex contends that this article was "highly material" because it provided a basis for understanding the likely activity of various molecules – by describing characteristics of protein receptors relevant to platelet aggregation – which a reasonable PTO examiner would have found important.

As explained above, the Court finds that the Colman article was not material. Apotex has thus failed to prove that Sanofi had any reason to mislead the PTO as to the true inventorship of the claimed invention. There is no evidence that any person with a duty of candor to the PTO intended to mislead the PTO, either by failing to disclose the Colman article or by not including Dr. Maffrand as a named inventor on the patent application.

Accordingly, Apotex has failed to show by clear and convincing evidence that Sanofi engaged or intended to engage in any inequitable conduct in its prosecution of the '265 patent.

IV. *Equitable Considerations*

The Supreme Court has reiterated that there is no rule that a permanent injunction "automatically follows" a determination that a patent has been infringed. *See eBay Inc. v. MercExchange, L.L.C.*, 547 U.S. ___, 126 S. Ct. 1837, 1840, 164 L. Ed. 2d 641 (2006). When a plaintiff seeks a permanent injunction in a patent case, a court must apply a traditional four factor test. Specifically, "[a] plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction." *Id.* at 1839. The decision to grant or deny permanent injunctive relief is "an act of equitable discretion" by the district court. *Id.*

In regard to the first two factors – irreparable injury and whether monetary damages are inadequate to make the patent holder whole – the Court concludes that both factors support the issuance of an injunction in this action. Sanofi has shown that it is likely to suffer irreparable price erosion, loss of goodwill, and a negative impact on the amount of research devoted to developing other medical uses for Plavix®. In regard to the third factor – i.e., whether "considering the balance of hardships between the

plaintiff and defendant, a remedy in equity is warranted" – the Court adheres to the analysis set forth upon issuing the preliminary injunction in this action, *see Sanofi-Synthelabo v. Apotex Inc.*, U.S. Dist. LEXIS 65127, at *75-78, and finds that the balance of hardships favors issuance of a permanent injunction. In regard to the fourth factor – i.e., "whether the public interest would not be disserved by a permanent injunction" – this involves essentially a balancing of the public interest in having access to generic drugs at reduced prices with the "significant public interest in encouraging the massive investment in research and development that is required before a new drug can be developed and brought to market." *Id.* at *80; *see Pfizer Inc. v. Teva Pharms. USA, Inc.*, 429 F.3d 1364, 1382 (Fed. Cir. 2005). As in its analysis at the preliminary injunction phase of this action, the Court finds that the competing, important public interests in this litigation are either in equipoise or slightly favor Sanofi. In sum, utilizing the four part test set forth in eBay to guide the Court's discretion once it has concluded – as it has here – that a patent has been infringed and is valid and enforceable, this Court concludes that a permanent injunction is appropriate in this action.

V. *Conclusion*

Apotex has concededly infringed Sanofi's '265 patent. This Court now finds that Apotex has failed to prove by clear and convincing evidence that the '265 patent is invalid or unenforceable and Sanofi is entitled to a permanent injunction prohibiting Apotex from further infringement. 35 U.S.C. § 271(e)(4)(B). Damages will be set in an amount to

be determined through future proceedings. 35 U.S.C. §§ 271(e)(4)(C).

Accordingly, judgment will be entered in favor of Sanofi. Apotex, Inc. and Apotex Corp. and their agents, servants, employees, and other representatives, and all persons acting in concert with them, are hereby permanently enjoined from engaging in any activity that infringes U.S. Patent No. 4,847,265.

Dated: New York, New York
June 19, 2007

SO ORDERED:

/s/ Sidney H. Stein
Sidney H. Stein, U.S.D.J.

APPENDIX C

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2007-1438

SANOFI-SYNTHELABO, SANOFI-SYNTHELABO, INC., and
BRISTOL-MYERS SQUIBB SANOFI PHARMACEUTICALS HOLDING PARTNERSHIP,

Plaintiffs-Appellees,

v.

APOTEX, INC. and APOTEX CORP.,

Defendants-Appellants.

[March 26, 2009]

Appeal from the United States District Court for the Southern District of New York in case no. 02-CV-2255, Judge Sidney H. Stein.

ORDER

A combined petition for panel rehearing and for rehearing en banc having been filed by the Appellants,* and a response thereto having been

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* Amicus Curiae, Golden Medical Supply, Inc. was granted leave to file a brief in support of the Appellants' combined petition for panel rehearing and rehearing en banc.

Apotex, Inc. and Apotex Corp. were granted leave to file a reply in support of their combined petition for panel rehearing and rehearing en banc.

invited by the court and filed by the Appellees, and the petition for rehearing and response, having been referred to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for panel rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for hearing en banc be, and the same hereby is, DENIED.

The mandate of the court will issue on April 2, 2009.

FOR THE COURT,

/s/ Jan Horbaly
Jan Horbaly
Clerk

Dated: 03/26/09

FILED
U.S. COURT OF APPEALS
FOR THE FEDERAL CIRCUIT
MAR 26 2009
JAN HORBALY
CLERK